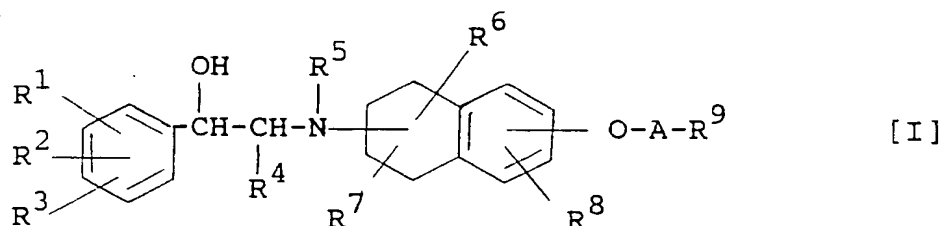




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(21) International Application Number: PCT/JP92/00449 (22) International Filing Date: 10 April 1992 (10.04.92) (30) Priority data: 9107827.9 12 April 1991 (12.04.91) GB (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only) : SHIOKAWA, Youichi [JP/JP]; 9-814, Hozumidai, Ibarake-shi, Osaka 567 (JP). NAGANO, Masanobu [JP/JP]; 4-6-19, Midoridai, Kanawishi-shi, Hyogo 666-01 (JP). TANIGUCHI, Kiyoshi [JP/JP]; 2-1-28, Minamiochiai, Suma-ku, Kobe-shi, Hyogo 654-01 (JP). TAKE Kazuhiko [JP/JP]; 3-3-2-201, Kouyoudai, Tondabayashi-shi, Osaka 584 (JP). KATO, Takeshi [JP/JP]; 12-27-302, Ooyacho, Nishinomiya-shi, Hyogo 663 (JP). TSUBAKI, Kazunori [JP/JP]; 1-1-C1-1213, Momoyamadai, Suita-shi, Osaka 565 (JP).		(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: ETHANOLAMINE DERIVATIVES WITH ANTI-POLLAQUIRIA ACTIVITY

**(57) Abstract**

This invention relates to new ethanolamine derivatives having gut selective sympathomimetic and anti-pollakiuria activities and represented by general formula (I), wherein R¹ is hydrogen or halogen, R² is halogen, hydroxy, protected hydroxy, aryloxy, lower alkoxy, halo(lower)alkoxy, nitro, cyano, amino or acylamino, R³ is hydrogen or halogen, R⁴ is hydrogen or lower alkyl, R⁵ is hydrogen or lower alkyl, R⁶ is hydrogen, hydroxy or lower alkyl, R⁷ is hydrogen or lower alkyl, R⁸ is hydrogen or halogen, R⁹ is carboxy or esterified carboxy, and A is lower alkylene, provided that R⁴ is lower alkyl; R⁵ is lower alkyl; R⁶ is hydroxy or lower alkyl; or R⁸ is halogen when R¹ is hydrogen, R² is halogen and R³ is hydrogen, and pharmaceutically acceptable salts thereof, to processes for the preparation thereof and to a pharmaceutical composition comprising the same.

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DESCRIPTION

ETHANOLAMINE DERIVATIVES WITH ANTI-POLLAKIURIA ACTIVITY

5 TECHNICAL FIELD

This invention relates to new ethanolamine derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

10 BACKGROUND ART

Some ethanolamine derivatives having spasmolytic activity and relaxing activity on smooth muscle contraction have been known as described, for example, in European Patent Application Publication Nos. 0 255 415, 15 0 303 546 and 0 383 686. However, it has not been known that they have an anti-pollakiuria activity.

DISCLOSURE OF INVENTION

This invention relates to new ethanolamine derivatives and pharmaceutically acceptable salts thereof. 20

More particularly, it relates to new ethanolamine derivatives and pharmaceutically acceptable salts thereof which have gut selective sympathomimetic and anti-pollakiuria activities, to processes for the preparation thereof, to a pharmaceutical composition 25 comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more particularly to a method for the treatment and/or 30 prevention of spasm or hyperanakisia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholangitis, urinary calculus and the like; and for the treatment 35 and/or prevention of dysuria such as pollakiuria, urinary

incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis or the like. Additionally, the object compound is
5 expected to be useful as therapeutical and/or preventive agents for obesity and glaucoma.

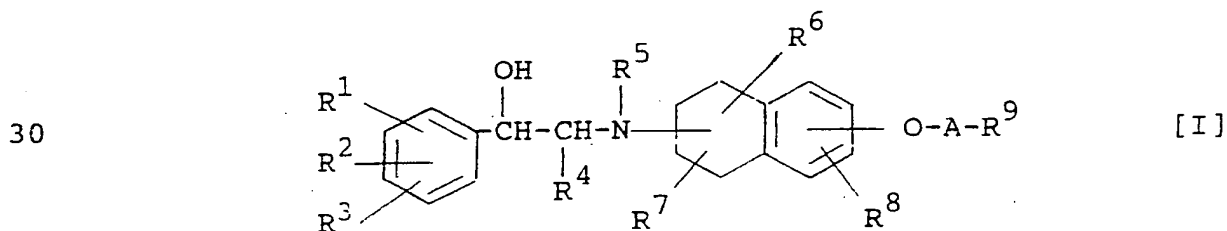
One object of this invention is to provide new and useful ethanolamine derivatives and pharmaceutically acceptable salts thereof which have gut selective
10 sympathomimetic and anti-pollakiuria activities.

Another object of this invention is to provide processes for the preparation of said ethanolamine derivatives and salts thereof.

A further object of this invention is to provide a
15 pharmaceutical composition comprising, as an active ingredient, said ethanolamine derivatives and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention
20 of aforesaid diseases in human beings or animals, using said ethanolamine derivatives and pharmaceutically acceptable salts thereof.

The object ethanolamine derivatives of this invention
25 are new and can be represented by the following general formula [I]:



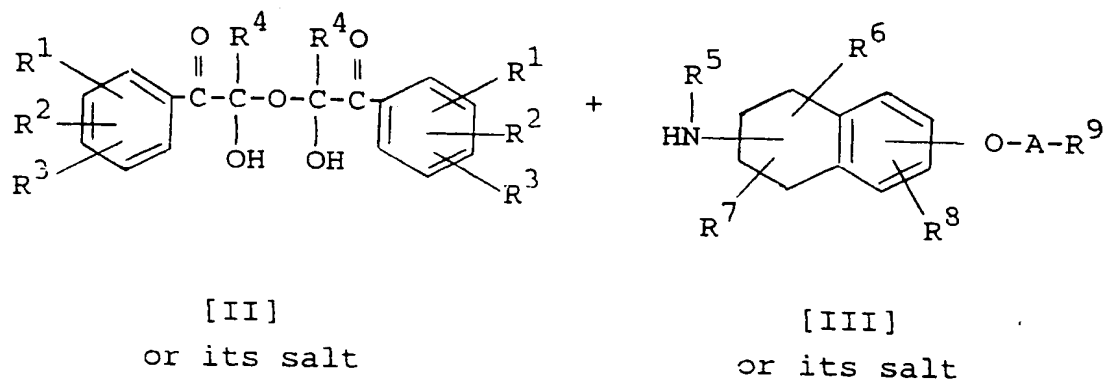
35

wherein R^1 is hydrogen or halogen,
 R^2 is halogen, hydroxy, protected hydroxy,
 aryloxy, lower alkoxy, halo(lower)alkoxy,
 nitro, cyano, amino or acylamino,
 R^3 is hydrogen or halogen,
 R^4 is hydrogen or lower alkyl,
 R^5 is hydrogen or lower alkyl,
 R^6 is hydrogen, hydroxy or lower alkyl,
 R^7 is hydrogen or lower alkyl,
 R^8 is hydrogen or halogen,
 R^9 is carboxy or esterified carboxy, and
 A is lower alkylene,
 provided that R^4 is lower alkyl; R^5 is lower
 alkyl; R^6 is hydroxy or lower alkyl; or R^8 is
 halogen when R^1 is hydrogen, R^2 is halogen and
 R^3 is hydrogen,

and pharmaceutically acceptable salts thereof.

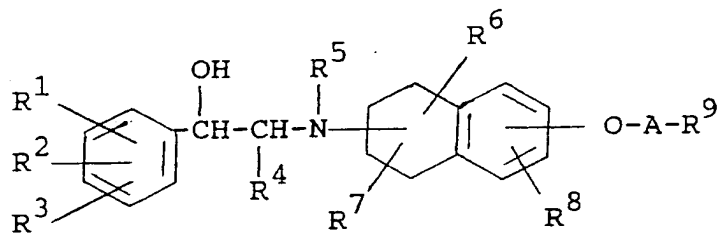
The object compound [I] or its salt can be prepared
 by the following processes.

Process 1



- 4 -

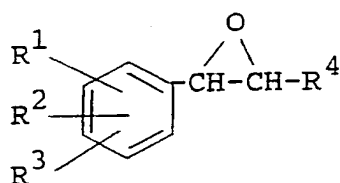
5



[I]
or its salt

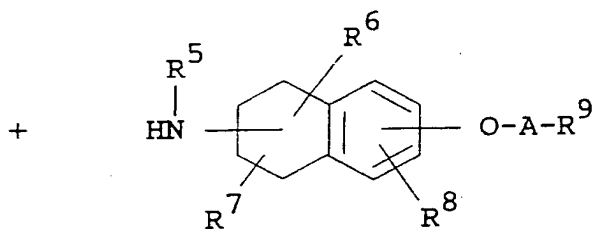
Process 2

10



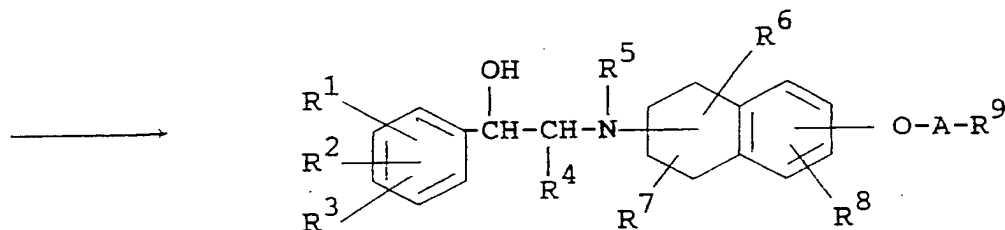
15

[IV]
or its salt



[III]
or its salt

20

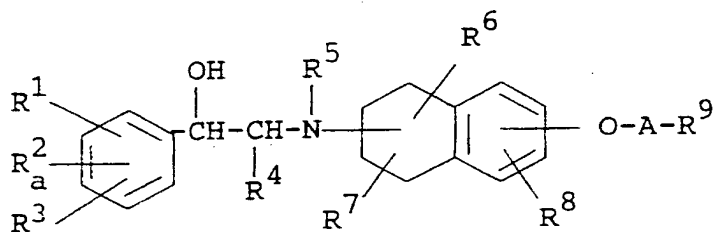


25

[I]
or its salt

Process 3

30

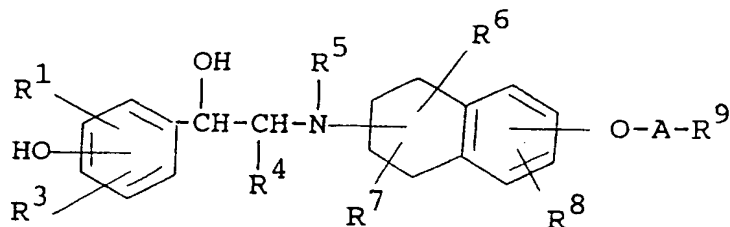


35

[Ia]
or its salt

elimination of
the hydroxy-
protective
group

5

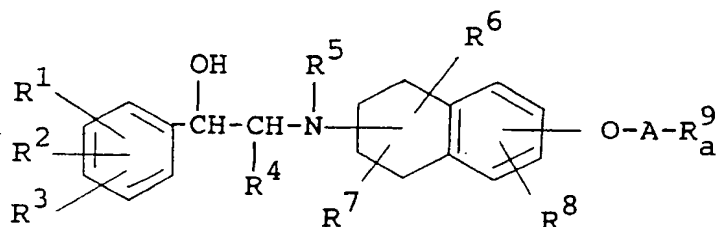


[Ib]
or its salt

10

Process 4

15

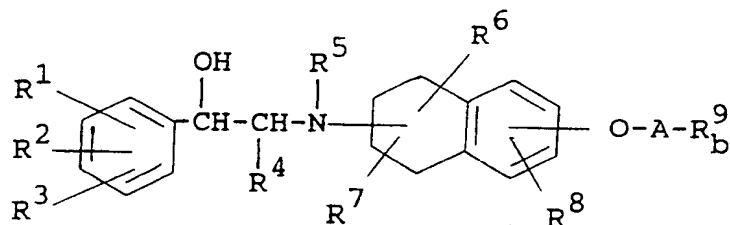


[Ic]
or its salt

20

25

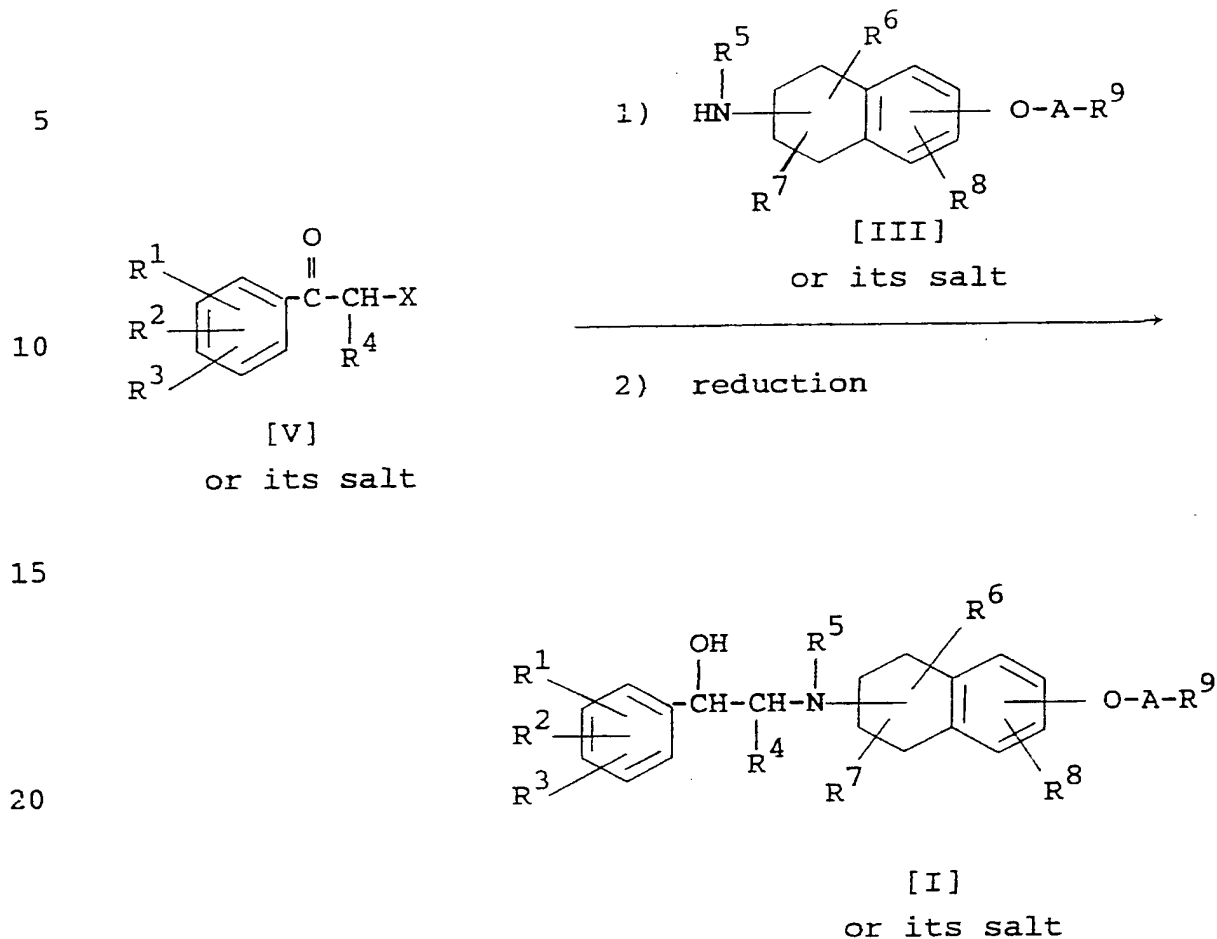
deesterification
→



[Id]
or its salt

30

35

Process 5

wherein $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9$ and A are each as defined above,
 R_{a9}^2 is protected hydroxy,
 R_{a9}^3 is esterified carboxy,
 R_{b9}^3 is carboxy, and
 X is halogen.

In the above and subsequent description of the present specification, suitable examples of the various definition to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "halogen" may be fluorine, chlorine, bromine, and iodine, in which preferable one is chlorine.

5 Suitable "lower alkylene" may be straight or branched one such as methylene, ethylene, trimethylene, propylene, pentamethylene, hexamethylene, ethylethylene or the like, in which preferable one is methylene.

10 Suitable "protected hydroxy" may be substituted lower alkoxy such as lower alkoxy(lower)alkoxy [e.g. methoxymethoxy, etc.], lower alkoxy(lower)alkoxy(lower)-alkoxy [e.g. methoxyethoxymethoxy, etc.], substituted or unsubstituted ar(lower)alkoxy [e.g. benzyloxy, nitrobenzyloxy, etc.], etc., acyloxy such as lower
15 alkanoyloxy [e.g. acetoxymethoxy, propionyl, pivaloyloxy, etc.], aroyloxy [e.g. benzoyloxy, fluorenylcarbonyloxy, etc.], lower alkoxycarbonyloxy [e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxy-
20 carbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyloxy [e.g. benzyloxycarbonyloxy, bromobenzyloxycarbonyloxy, etc.] etc., tri(lower)-alkylsilyloxy [e.g. trimethylsilyloxy, etc.] and the like.

25 The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or
30 unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and
35 the like, in which preferable one is lower alkoxycarbonyl.

Suitable "lower alkyl" and lower alkyl moiety in the term "lower alkylsulfonyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl or the like, in which preferable one is methyl.

Suitable "lower alkoxy" and lower alkoxy moiety in the term "halo(lower)alkoxy" may be methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy and the like, in which preferable one is methoxy.

Suitable acyl moiety in the term "acylamino" may be carboxy, esterified-carboxy, lower alkanoyl, carbamoyl optionally substituted with lower alkyl, lower alkylsulfonyl and the like, in which preferable one is lower alkylsulfonyl.

Suitable "lower alkylsulfonyl" may be methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like, in which preferable one is methylsulfonyl.

Suitable "lower alkanoyl" may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like.

Suitable "halo(lower)alkoxy" may be chloromethoxy, fluoromethoxy, bromomethoxy, difluoromethoxy, dichloromethoxy, trifluoromethoxy, trichloromethoxy, 2-fluoroethoxy and the like, in which preferable one is trifluoromethoxy.

Suitable "aryloxy" may be phenoxy, tolyloxy, xylyloxy, naphthyloxy and the like, in which preferable one is phenoxy.

Suitable "N-protective group" may be substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amylloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or

unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, aralkyl [e.g. trityl, benzyl, etc.] or the like.

5 Suitable "acid residue" may be halogen [e.g. fluoro, chloro, bromo, iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethanesulfonyloxy, etc.], and the like, in which preferable one is halogen.

10 Preferable compound [I] is one which has halogen for R^1 and hydroxy or protected hydroxy for R^2 , or hydrogen for R^1 and halogen for R^2 ; hydrogen for R^3 ; hydrogen for R^4 ; hydrogen for R^5 ; hydrogen or hydroxy for R^6 ; hydrogen for R^7 ; hydrogen for R^8 ; esterified carboxy for R^9 ; and lower alkylene for A provided that R^6 is hydroxy when R^1 is hydrogen and R^2 is halogen.

15 Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an
20 organic acid addition salt [e.g. formate, acetate, trifluoroacetate, oxalate, maleate, fumarate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

25 The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

30 The compound [I] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its salt in the presence of a reducing agent.

 Suitable salts of the compounds [II] and [III] may be the same as those exemplified for the compound [I].

35 Suitable reducing agent may be borohydride compound such as alkali metal borohydride [e.g. sodium borohydride,

sodium cyanoborohydride, lithium cyanoborohydride, lithium triethylborohydride, etc.], tetrabutylammonium cyanoborohydride or the like, in which preferable one is alkali metal borohydride.

5 The reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium
10 bicarbonate, potassium bicarbonate, etc.], tri(lower)-alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline or the like.

 The reaction is usually carried out in a conventional solvent, such as water, an alcohol [e.g. methanol,
15 ethanol, propanol, isopropanol, etc.], dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

20

Process 2

 The compound [I] or its salt can be prepared by reacting a compound [IV] or its salt with a compound [III] or its salt.

25 Suitable salt of the compound [IV] may be an alkali metal salt as exemplified for the compound [I].

 The reaction is preferably carried out in the presence of a base. Suitable base may be referred to those as explained in Process 1.

30 The reaction is usually carried out in a conventional solvent, such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction.

35 The reaction temperature is not critical, and the

reaction can be carried out under cooling to heating.

Process 3

5 The compound [Ib] or its salt can be prepared by
subjecting a compound [Ia] or its salt to elimination
reaction of the hydroxy-protective group.

This reaction is carried out in accordance with a
conventional method such as hydrolysis, reduction or the
like.

10 The hydrolysis is preferably carried out in the
presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an
organic base such as an alkali metal [e.g. sodium,
potassium, etc.], an alkaline earth metal [e.g. magnesium,
15 calcium, etc.], the hydroxide or carbonate or bicarbonate
thereof, trialkylamine [e.g. trimethylamine,
triethylamine, etc.], picoline 1,5-diazabicyclo[4.3.0]-
non-5-ene, 1,4-diazabicyclo[2.2.2]octane,
1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

20 Suitable acid may include an organic acid [e.g.
formic acid, acetic acid, propionic acid, trichloroacetic
acid, trifluoroacetic acid, methanesulfonic acid,
p-toluenesulfonic acid, etc.] and an inorganic acid [e.g.
hydrochloric acid, hydrobromic acid, sulfuric acid,
25 hydrogen chloride, hydrogen bromide, hydrogen fluoride,
etc.].

The reaction is usually carried out in a solvent such
as water, an alcohol [e.g. methanol, ethanol, etc.],
methylene chloride, chloroform, tetrachloromethane,
30 tetrahydrofuran, a mixture thereof or any other solvent
which does not adversely influence the reaction. A liquid
base or acid can be also used as the solvent. The
reaction temperature is not critical and the reaction is
usually carried out under cooling to heating.

35 The reduction method applicable for the elimination

reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

In this reaction, in case that the hydroxy-protective group is benzyl, the reduction can be also carried out in the presence of a combination of palladium catalyst [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent,

and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

5 The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

10 In this reaction, in case that the compound [Ia] having halogen for R^1 and/or halogen for R^3 and/or esterified carboxy for R^9 is used as a starting compound, the compound [Ib] having hydrogen for R^1 and/or hydrogen for R^3 and/or carboxy for R^9 may be obtained according to reaction conditions. This case is included within the scope of the present reaction.

Process 4

15 The compound [Id] or its salt can be prepared by subjecting a compound [Ic] or its salt to deesterification reaction.

20 This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and the reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

25 In this reaction, in case that the compound [Ic] having protected hydroxy for R^2 is used as a starting compound, the compound [Id] having hydroxy for R^2 may be obtained according to reaction conditions. This case is included within the scope of the present reaction.

Process 5

30 The compound [I] or its salt can be prepared by the following method. Namely, 1) the compound [V] or its salt is firstly reacted with a compound [III] or its salt, and then 2) subjecting the resultant product to reduction.

35 Suitable salt of the compound [V] may be the same as those exemplified for the compound [I].

In the first step, the reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, pyridine or the like.

The reaction is usually carried out in a conventional solvent such as water, an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], dioxane or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

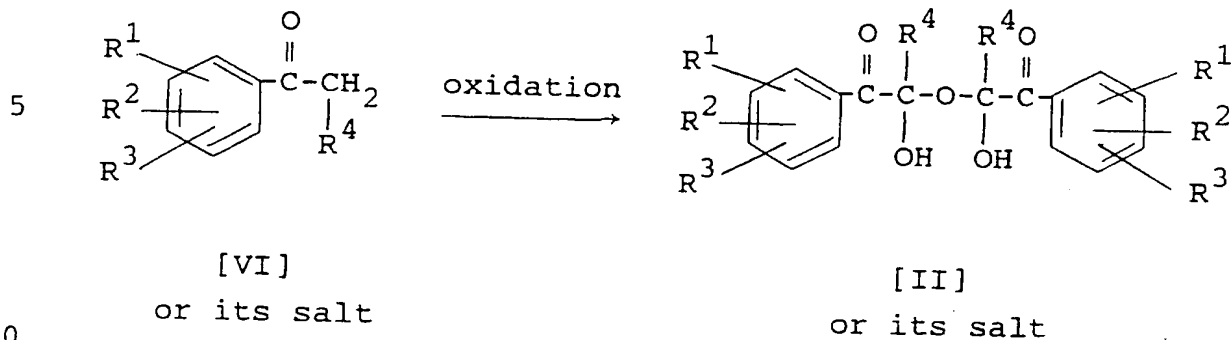
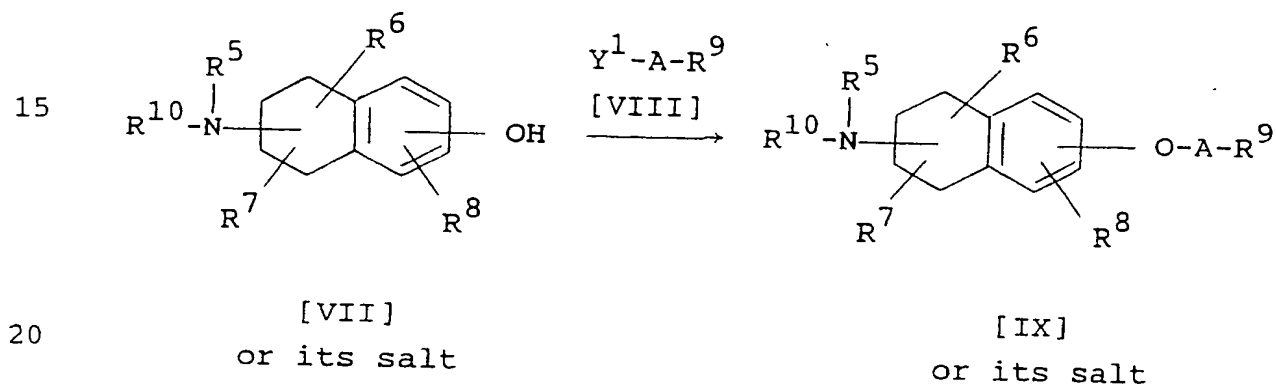
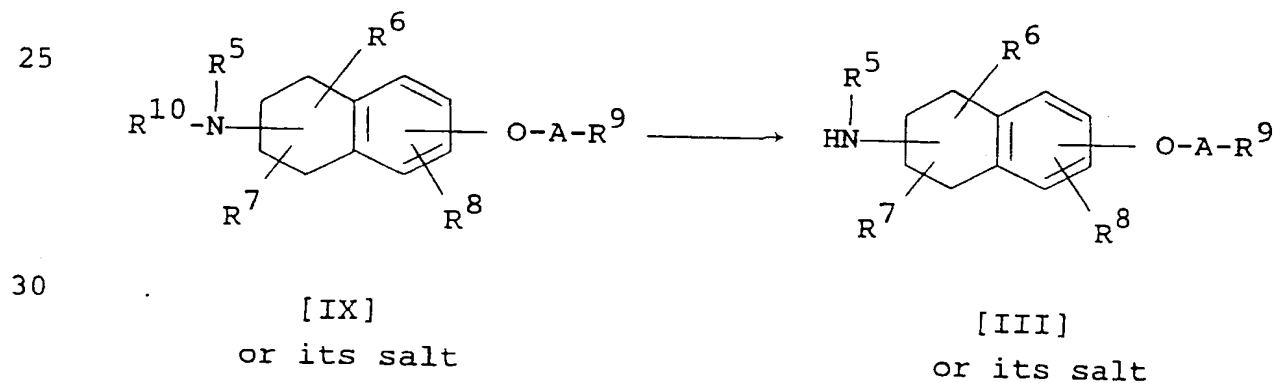
The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

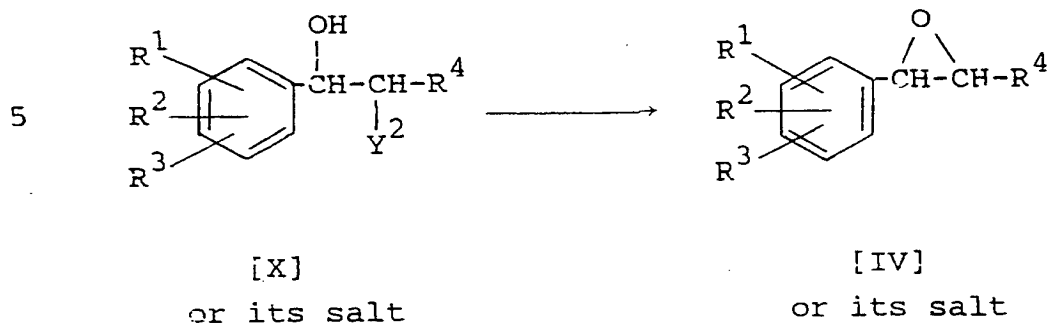
In the second step, suitable reducing agent to be used in this reduction may be the same as those exemplified in Process 1.

The reaction is usually carried out in a conventional solvent, such as water, an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], dioxane, tetrahydrofuran or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

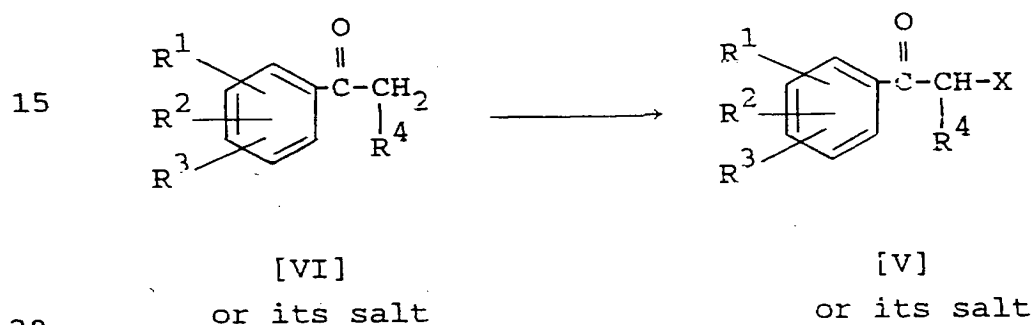
The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

The starting compounds [II], [III], [IV] and [V] or salts thereof can be prepared by the following processes.

Process AProcess BProcess C

Process D

10

Process E

20

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , A and X are
each as defined above,

25 R^{10} is an N-protective group,
 Y^1 is acid residue, and
 Y^2 is acid residue.

30 The above-mentioned processes for preparing the
starting compounds [II], [III], [IV] and [V] are explained
in detail in the following.

35

Process A

The compound [II] or its salt can be prepared by subjecting a compound [VI] or its salt to oxidation.

5 Suitable salt of the compound [VI] may be the same as those exemplified for the compound [I].

 Suitable oxidizing agent to be used in this oxidation may be selenium dioxide and the like.

10 The reaction is usually carried out in a conventional solvent such as water, dioxane, acetic anhydride or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

 The reaction temperature is not critical, and the reaction is usually carried out under heating.

15 Process B

 The compound [IX] or its salt can be prepared by reacting a compound [VII] or its salt with a compound [VIII].

20 Suitable salts of the compounds [VII] and [IX] may be the same as those exemplified for the compound [I].

 When the compound [VIII] having halogen for Y¹ is used in this reaction, the reaction is preferably carried out in the presence of a base such as alkali metal [e.g. lithium, sodium, potassium, etc.], the hydroxide or
25 carbonate or bicarbonate thereof [e.g. sodium hydroxide, potassium carbonate, potassium bicarbonate, etc.], alkaline earth metal [e.g. calcium, magnesium, etc.], alkali metal hydride [e.g. sodium hydride, etc.], alkaline
30 earth metal hydride [e.g. calcium hydride, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], alkaline earth metal
alkoxide [e.g. magnesium methoxide, magnesium ethoxide, etc.] or the like, or alkali metal iodide [e.g. sodium
iodide, potassium iodide, etc.] and the like.

35 Additionally, the reaction is also preferably carried

out in the presence of phase transfer catalyst [e.g. tetra-n-butylammonium bromide, etc.].

This reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, aromatic hydrocarbon [e.g. benzene, toluene, xylene, etc.], N,N-dimethylformamide, acetone, a mixture thereof, or any other solvent which does not adversely influence the reaction. Additionally, in case that the compound [VIII] is in liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process C

The compound [III] or its salt can be prepared by subjecting a compound [IX] or its salt to elimination reaction of the N-protective group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine

hydrochloride, etc.].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the

like.

In case that the N-protective group is benzyl, the reduction is preferably carried out in the presence of a combination of palladium catalyst [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process D

The compound [IV] or its salt can be prepared by reacting a compound [X] or its salt with a base.

Suitable salt of the compound [X] may be the same as those exemplified for the compound [I].

Suitable base may be referred to those as explained in Process B.

The reaction is usually carried out in a conventional solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process E

The compound [V] or its salt can be prepared by subjecting a compound [VI] or its salt to halogenation reaction.

5 Suitable salt of the compound [VI] may be the same as those exemplified for the compound [I].

10 Suitable halogenating agent to be used in this reaction may be chlorine, bromine, N-bromosuccinimide, N-chlorosuccinimide, a combination of trimethylbromosilane and dimethyl sulfoxide, tetrabutylammonium tribromide, hydrogen halide [e.g. hydrogen bromide, hydrogen chloride, etc.] and the like.

15 The reaction is usually carried out in a conventional solvent such as water, acetic acid, tetrachloromethane, chloroform, dichloromethane, dimethoxyethane, tetrahydrofuran, acetonitrile or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

20 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

25 The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like, and converted to the desired salt in conventional manners, if necessary.

30 It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

35 The object compound [I] and pharmaceutically acceptable salts thereof possess gut selective sympathomimetic and anti-pollakiuria activities, and are useful for the treatment and/or prevention of gastrointestinal disorders caused by smooth muscle

contractions in human beings or animals, and more particularly to methods for the treatment and/or prevention of spasm or hyperanakinnesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholangitis, urinary calculus and the like; and for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis or the like. Additionally, the object compound is expected to be useful as therapeutical and/or preventive agents for obesity and glaucoma.

In order to illustrate the usefulness of the object compound [I], the pharmacological data of the compound [I] are shown in the following.

Test 1

Effect on isolated rat distal colon :

(i) Test Method :

Male SD rats (180~230 g) were used. Animals were fasted for 24 hours prior to experiment. Distal colon was removed immediately after sacrifice and placed in an organ bath containing 25 ml Tyrode solution aerating with 95% O₂, 5% CO₂ at 37°C. The strip was mounted under 0.5 g tension and spontaneous contractions were recorded isometrically. After the motility was of a uniform size, test compound was added to an organ bath and the contractions were observed over a 30 minutes period. Effect of test compound was calculated by comparing contractions before and after test compound.

(ii) Test Results :

Test Compound (Example No.)	IC ₅₀ (M)
1	8.0×10^{-10}
2	1.9×10^{-9}

Test 2

Effect on isolated non-pregnant rat uterus :

(i) Test Method :

Female SD rats (150~180 g) were used. 48 and 24 hours prior to use, rats were given estradiol (ovahormon benzoat : Trademark, Teikoku Hormone Mfg. Co., Ltd.) subcutaneously at a dose of 40 µg/rat to induce oestrus. The animals were killed and uterine horns were removed. Each strip was placed in an organ bath containing 25 ml Locke solution aerating with 95% O₂, 5% CO₂ at 37°C under 1 g tension. Contractions were recorded isometrically. After the spontaneous contractions were of a uniform size, test compound was added to organ bath. The motility was observed over a 20 minutes period. Effect of test compound was calculated by comparing contractions before and after test compound.

(ii) Test Results :

Test Compound (Example No.)	IC ₅₀ (M)
1	3.2×10^{-7}
2	5.1×10^{-7}

Test 3

Effect on cystometrograph

(i) Test Method :

5 Male S.D. rats, aged 7-8 weeks, were anesthetized with ether and placed supine on a board. After a midline incision in the abdomen, the bladder was exposed. Polyethylene catheters, which were used to measure the intravesical pressure and to infuse xylene and saline, 10 were inserted into the bladder through a small incision at the apex of the bladder dome. The rats were placed in a restraining cage and were allowed to recover from anesthesia for about 3 hours. The bladder catheters were connected to an infusion pump and a pressure transducer 15 respectively. 30% xylene (silicone oil solution) was infused at a rate of 3.3 ml/hr for 1 hour and then saline was infused at same rate.

Cystometrography was performed at 30 minutes intervals for 2 hours. The bladder capacity (volume) was 20 calculated from the time required to fill the bladder..

Test compound was administered intravenously via femoral artery.

(ii) Test Results : (relative % of control)

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Time \ Group (minutes)	Normal	Vehicle	Test Compound Example 4 Dose: 1.0mg/kg
Before	100	100	100
0-30	99.3	99.8	153.4
30-60	98.1	106.5	143.0
60-90	98.7	104.6	148.9
90-120	95.3	111.5	156.9

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral, parenteral or external (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solutions, suspension, emulsion, ointment, gel, ophthalmic solutions, and the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

A mixture of 3'-chloro-4'-hydroxyacetophenone (521 mg) and selenium dioxide (444 mg) in dioxane (20 ml) and water (0.08 ml) was stirred under reflux for 6 hours and filtered. The filtrate was concentrated in vacuo and extracted with diethyl ether. The extract was washed twice with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give colorless crystals of 2,2'-

oxybis[3'-chloro-2,4'-dihydroxyacetophenone] (334 mg).

mp : 137-140°C

IR (Nujol) : 3360, 3180, 3100, 1685, 1680 cm⁻¹

5 NMR (DMSO-d₆, δ) : 5.87 (2H, d, J=9Hz), 7.04 (2H, d, J=8.5Hz), 7.45 (2H, d, J=9Hz), 7.90 (2H, dd, J=2 and 8.5Hz), 8.04 (2H, d, J=2Hz), 11.32 (2H, br s)

MASS (m/z) : 369 (M⁺-OH), 155

10 Preparation 2

To a solution of trans-2-amino-1,2,3,4-tetrahydronaphthalene-1,7-diol (0.40 g), triethylamine (0.68 ml), in N,N-dimethylformamide (8 ml) was added di-tert-butyl dicarbonate (0.54 g). After stirring for 4
15 hours at ambient temperature, the reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. A mixture of chloroform and
20 methanol (20:1) was added to the residue, and the resulting precipitate was collected and dried to afford trans-2-(tert-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-1,7-diol (0.38 g). Further product was obtained (0.26 g) from the filtrate after column
25 chromatography on silica gel (eluent:chloroform-methanol = 20:1).

mp : 182-184°C

IR (Nujol) : 3370, 3280, 1660 cm⁻¹

30 NMR (DMSO-d₆, δ) : 1.39 (9H, s), 1.4-1.8 (1H, m), 1.8-2.0 (1H, m), 2.5-2.7 (2H, m), 3.3-3.6 (1H, m), 4.29 (1H, t-like, J=ca. 8Hz), 5.18 (1H, d, J=8Hz), 6.54 (1H, dd, J=2 and 8Hz), 6.6-6.8 (1H, m), 6.82 (1H, d, J=2Hz), 6.85 (1H, s), 9.06 (1H, s)

35 MASS (m/z) : 223 ((M⁺+1)-57)

Preparation 3

To an ice-cooled mixture of trans-2-(tert-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-1,7-diol (0.38 g), potassium carbonate (0.28 g), and acetone (1.4 ml) was added ethyl bromoacetate (0.23 ml). After stirring for 20 hours at ambient temperature, the reaction mixture was diluted with ethyl acetate. The insoluble precipitate which formed was filtered off and washed with ethyl acetate. Removal of the solvent and purification of the residue by column chromatography on silica gel (eluent:chloroform-ethyl acetate = 10:1) afforded trans-2-(tert-butoxycarbonylamino)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthol (0.44 g).

mp : 129-130°C

IR (Nujol) : 3500, 3360, 1715, 1670 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J=7\text{Hz}$), 1.40 (9H, s), 1.4-1.8 (1H, m), 1.8-2.0 (1H, m), 2.6-2.8 (2H, m), 3.3-3.6 (1H, m), 4.15 (2H, q, $J=7\text{Hz}$), 4.33 (1H, t-like, $J=\text{ca. } 8\text{Hz}$), 4.70 (2H, s), 5.30 (1H, d, $J=7\text{Hz}$), 6.6-6.8 (2H, m), 6.9-7.0 (2H, m)

MASS (m/z) : 309 ($(\text{M}^++1)-57$)

Preparation 4

To a solution of trans-2-(tert-butoxycarbonylamino)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthol (0.26 g) in ethanol (7.0 ml) was added 5N hydrogen chloride in ethanol (3.5 ml). After stirring for 3 hours at ambient temperature, the reaction mixture was concentrated in vacuo. Toluene was added to the residue, and the mixture was concentrated to afford trans-2-amino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthol hydrochloride (0.21 g).

mp : 135-137°C

IR (Nujol) : 3250, 3150, 1730 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.22 (3H, t, $J=7\text{Hz}$), 1.7-2.0 (1H,

- 28 -

m), 2.0-2.2 (1H, m), 2.7-2.9 (2H, m), 3.0-3.2 (1H, m), 4.16 (2H, q, J=7Hz), 4.59 (1H, t-like, J=ca. 8Hz), 4.73 (2H, s), 6.16 (1H, d, J=7Hz), 6.78 (1H, dd, J=2 and 8Hz), 6.9-7.1 (2H, m), 8.32 (3H, br s)

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MASS (m/z) : 265

Preparation 5

A mixture of 2,3'-dichloro-4'-hydroxyacetophenone (3.77 g), 2-methoxyethoxymethyl chloride (3.44 g), and potassium carbonate (2.80 g) in N,N-dimethylformamide (38 ml) was stirred at ambient temperature for 3.5 hours, then diluted with water, and extracted with ethyl acetate. The extract was washed twice with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel) using a mixture of toluene and ethyl acetate to give an oil of 2,3'-dichloro-4'-(2-methoxyethoxymethoxy)acetophenone (4.03 g).

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20 IR (Film) : 1695, 1685, 1245, 1200, 1165, 1135, 1105 cm⁻¹

NMR (CDCl₃, δ) : 3.37 (3H, s), 3.56 (2H, m), 3.88 (2H, m), 4.63 (2H, s), 5.44 (2H, s), 7.31 (1H, d, J=8.5Hz), 7.84 (1H, dd, J=2 and 8.5Hz), 8.02 (1H, d, J=2Hz)

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Preparation 6

A solution of 2,3'-dichloro-4'-(2-methoxyethoxymethoxy)acetophenone (4.40 g) in tetrahydrofuran (12 ml) and a solution of borane in tetrahydrofuran (1.0M, 9.0 ml) were added simultaneously to a mixture of a solution of (R)-tetrahydro-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]-oxazaborole in tetrahydrofuran (ca. 0.5M, 1.20 ml) and a solution of borane in tetrahydrofuran (1.0M, 1.50 ml) at 15-25°C under nitrogen over 30 minutes. The resulting

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mixture was stirred at the same temperature for 2 hours, and then methanol (3.6 ml) was added dropwise to the mixture under ice cooling. The mixture was stirred at ambient temperature and concentrated in vacuo. The residue was partitioned between diethyl ether and 0.5N hydrochloric acid. The organic layer was separated, washed with brine, sodium bicarbonate aqueous solution, and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene and ethyl acetate to give an oil containing (-)-1-[3-chloro-4-(2-methoxyethoxymethoxy)phenyl]-2-chloroethanol (4.18 g); $[\alpha]_D^{19.6} = -26.46^\circ$ (C=0.99, CH₂Cl₂).

The obtained oil (4.18 g), isopropenyl acetate (2.84 g), and lipase PS Amano prepared by Amano Pharmaceutical Co., Ltd. (6.44 g) in dry diisopropyl ether (134 ml) was stirred at ambient temperature for 15 hours and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel using a mixture of toluene and ethyl acetate to give an oil of (-)-1-[3-chloro-4-(2-methoxyethoxymethoxy)phenyl]-2-chloroethanol (3.62 g).

$$[\alpha]_D^{17.6} = -29.90^\circ \text{ (C=0.993, CH}_2\text{Cl}_2\text{)}$$

IR (Film) : 3400, 1240, 1105, 1080 cm⁻¹

NMR (CDCl₃, δ) : 2.64 (1H, br s), 3.37 (3H, s), 3.54-3.75 (4H, m), 3.85-3.90 (2H, m), 4.84 (1H, quartet, J=3.5 and 8Hz), 5.34 (2H, s), 7.22 (2H, m), 7.43 (1H, d, J=1Hz)

30 Preparation 7

A mixture of (-)-1-[3-chloro-4-(2-methoxyethoxymethoxy)phenyl]-2-chloroethanol (4.38 g), 1N sodium hydroxide aqueous solution (29.7 ml), and diethyl ether (29.7 ml) was stirred at ambient temperature for 4 hours, saturated with sodium sulfate, and extracted four

times with n-hexane. The extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure to give a colorless oil of (+)-[3-chloro-4-(2-methoxyethoxymethoxy)phenyl]oxirane (3.79 g).

5 $[\alpha]_D^{18.4} = +22.40^\circ$ (C=1.25, benzene)

IR (Film) : 1235, 1105 cm^{-1}

10 NMR (CDCl_3 , δ) : 2.76 (1H, quartet, J=2.5 and 5.5Hz), 3.12 (1H, quartet, J=4 and 5.5Hz), 3.37 (3H, s), 3.56 (2H, m), 3.79 (1H, quartet, J=2.5 and 4Hz), 3.87 (2H, m), 5.34 (2H, s), 7.12 (1H, quartet, J=2 and 8.5Hz), 7.21 (1H, d, J=8.5Hz), 7.28 (1H, d, J=2Hz)

MASS (m/z) : 258 (M^+), 89 (base), 59

15 Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 1.

20 1) 2,2"-Oxybis[4'-benzyloxy-3'-chloro-2-hydroxyacetophenone]

mp : 116-123.5°C

IR (Nujol) : 3410, 3330, 1680, 1280 cm^{-1}

25 NMR (DMSO-d_6 , δ) : 5.33 (4H, s), 5.90 (2H, d, J=9Hz), 7.3-7.55 (12H, m), 7.57 (2H, d, J=9Hz), 8.03 (2H, dd, J=9 and 2Hz), 8.10 (2H, d, J=2Hz)

FAB-MASS (m/z) : 549 ($\text{M}^+ - \text{H}_2\text{O} + 1$)

30 2) 2,2"-Oxybis[3'-chloro-2-hydroxy-4'-methoxyacetophenone]

mp : 98-104°C

IR (Nujol) : 3370, 1685, 1280 cm^{-1}

35 NMR (DMSO-d_6 , δ) : 3.95 (6H, s), 5.80 and 5.90 (2H, d, J=9Hz), 7.2-7.3 (2H, m), 7.48 and 7.57 (2H, d, J=9Hz), 7.95-8.1 (4H, m)

FAB-MASS (m/z) : 397 ($\text{M}^+ - \text{H}_2\text{O} + 1$)

- 3) 2,2''-Oxybis[2-hydroxy-3'-phenoxyacetophenone]
IR (Film) : 3430, 1680, 1300-1200 cm^{-1}
NMR (CDCl_3 ; δ) : 4.51 (2H, d, $J=10\text{Hz}$), 6.10 (2H, d, $J=10\text{Hz}$), 7.0-7.9 (18H, m)

- 4) 2,2''-Oxybis[3'-chloro-2-hydroxy-4'-methanesulfonylaminoacetophenone]

(This compound was used for the next step without purification.)

Preparation 9

The following compound was obtained according to a similar manner to that of Preparation 6.

(-)-1-(4-Benzyloxy-3-chlorophenyl)-2-chloroethanol

mp : 86-88°C

$[\alpha]_{\text{D}}^{29} = -28.26^\circ$ ($C=0.895$, CH_2Cl_2)

IR (Nujol) : 3370, 3300, 1260 cm^{-1}

NMR (CDCl_3 , δ) : 2.36 (1H, br), 3.5-3.75 (2H, m), 4.82 (1H, m), 5.16 (2H, s), 6.95 (1H, d, $J=8.5\text{Hz}$), 7.19 (1H, dd, $J=8.5$ and 2Hz), 7.25-7.5 (6H, m)

Preparation 10

The following compound was obtained according to a similar manner to that of Preparation 7.

(+)-(4-Benzyloxy-3-chlorophenyl)oxirane

mp : 79-84°C

$[\alpha]_{\text{D}}^{28.8} = +19.50^\circ$ ($C=1.02$, benzene)

IR (Nujol) : 1265, 1240 cm^{-1}

NMR (CDCl_3 , δ) : 2.76 (1H, dd, $J=5.5$ and 2.5Hz), 3.11 (1H, dd, $J=5.5$ and 4Hz), 3.78 (1H, dd, $J=4$ and 2.5Hz), 5.16 (2H, s), 6.93 (1H, d, $J=8.5\text{Hz}$),

7.10 (1H, dd, J=8.5 and 2Hz), 7.25-7.5 (6H, m)

Preparation 11

A suspension of 3-chloro-4-hydroxyacetophenone (34.12 g), benzylbromide (34.21 g), and potassium carbonate (38.70 g) in N,N-dimethylformamide (171 ml) was stirred at ambient temperature for 5 hours and filtered. The filtrate was evaporated in vacuo and the residue was partitioned between methylene chloride and water. The methylene chloride layer was separated, washed with 5% sodium hydroxide solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was washed with a mixture of n-hexane and toluene to give a pale yellow powder of 4'-benzyloxy-3'-chloroacetophenone (40.23 g).

mp : 112-115°C

IR (Nujol) : 1665, 1270 cm^{-1}

NMR (CDCl_3 , δ) : 2.54 (3H, s), 5.23 (2H, s), 7.00 (1H, d, J=8.5Hz), 7.25-7.5 (5H, m), 7.82 (1H, dd, J=8.5 and 2Hz), 8.01 (1H, d, J=2Hz)

MASS (m/z) : 260 (M^+), 91 (base)

Preparation 12

Bromine (27.69 g) was added dropwise to a solution of 4'-benzyloxy-3'-chloroacetophenone (43.02 g) in dimethoxyethane (430 ml) at ambient temperature over 1 hour and the mixture was stirred at the same temperature for 2 hours. After evaporation, the resulting residue was dissolved in methylene chloride, washed with sodium hydrogen carbonate aqueous solution and brine, dried over magnesium sulfate. The solution was evaporated in vacuo and the residue was triturated with a mixture of n-hexane and ethyl acetate to afford 4'-benzyloxy-2-bromo-3'-chloroacetophenone (41.45 g).

mp : 114-118°C

IR (Nujol) : 1675, 1190 cm^{-1}

NMR (CDCl_3 , δ) : 4.36 (2H, s), 5.24 (2H, s), 7.02 (1H, d, $J=8.5\text{Hz}$), 7.25-7.5 (5H, m), 7.85 (1H, dd, $J=8.5$ and 2Hz), 8.04 (1H, d, $J=2\text{Hz}$)

MASS (m/z) : 339 (M^++1), 338 (M^+), 91 (base)

Preparation 13

A solution of 4'-benzyloxy-2-bromo-3'-chloroacetophenone (41.08 g) and tetra-n-butylammonium bromide (3.90 g) in 1,2-dichloroethane (973 ml) was refluxed for 6 hours, evaporated in vacuo, and extracted with dichloromethane. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from a mixture of diisopropyl ether and ethyl acetate to afford 4-benzyloxy-2,3'-dichloroacetophenone (31.38 g).

mp : 114-117.5°C

IR (Nujol) : 1685, 1205 cm^{-1}

NMR (CDCl_3 , δ) : 4.62 (2H, s), 5.25 (2H, s), 7.03 (1H, d, $J=8.5\text{Hz}$), 7.3-7.5 (5H, m), 7.83 (1H, dd, $J=8.5$ and 2Hz), 8.02 (1H, d, $J=2\text{Hz}$)

MASS (m/z) : 294 (M^+), 91 (base)

Preparation 14

To an ice-cooled solution of potassium t-butoxide (0.64 g) in tetrahydrofuran (5.2 ml) was added a solution of trimethylsulfonium iodide (1.2 g) in dimethyl sulfoxide (5.2 ml). During the addition, the reaction temperature was maintained below 5°C. After the addition was complete, 3-trifluoromethoxybenzaldehyde (1.05 g) was added to the reaction mixture. After 5 minutes stirring, the reaction mixture was poured into water, and extracted once with ethyl acetate. The extract was washed twice with water and once with brine, dried over anhydrous sodium sulfate, and evaporated in vacuo to give

3-trifluoromethoxyphenyloxirane (1.1 g).

This compound was used for the next step without further purification.

5 NMR (CDCl₃, δ) : 2.7-2.8 (1H, m), 3.1-3.2 (1H, m),
3.8-3.9 (1H, m), 7.1-7.5 (4H, m)

MASS (m/z) : 204

Preparation 15

10 A mixture of 7-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (3.0 g),
diphenylphosphoryl azide (2.93 ml) and triethylamine (1.90 ml) in tert-butanol (60 ml) was refluxed for 1.5 hours.
After cooling, the mixture was evaporated in vacuo. To the residue were added ethyl acetate and water, and the
15 organic layer was separated, washed with saturated sodium hydrogencarbonate and brine, dried over sodium sulfate,
and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of
n-hexane and ethyl acetate (50:1) as an eluent to afford
20 7-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl isocyanate (2.33 g) as an oil.

IR (Film) : 2250 cm⁻¹

25 NMR (CDCl₃, δ) : 1.48 (3H, s), 1.68-1.89 (1H, m),
1.91-2.09 (1H, m), 2.65-3.06 (4H, m), 3.77 (3H, s), 6.57 (1H, d, J=2.7Hz), 6.73 (1H, dd, J=2.7
and 8.4Hz), 7.04 (1H, d, J=8.4Hz)

MASS (m/z) : 217 (M⁺)

Preparation 16

30 To a solution of 7-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl isocyanate (192 mg) in tetrahydrofuran (5 ml) and tert-butanol (0.2 ml) was added sodium hydride (60% dispersion in oil; 42 mg) at 0°C and the mixture was refluxed for 15 minutes. After cooling,
35 brine was added to the mixture. The organic layer was

separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of n-hexane and ethyl acetate (10:1) as an eluent to afford N-tert-butoxycarbonyl-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (258 mg) as an oil.

IR (Film) : 3430, 3350, 1700 cm^{-1}

NMR (CDCl_3 , δ) : 1.42 (9H, s), 1.44 (3H, s), 1.50-1.78 (1H, m), 2.27-2.48 (1H, m), 2.74 (2H, pseudo t, $J=6.5\text{Hz}$), 2.84 (2H, s), 3.77 (3H, s), 4.45 (1H, br s), 6.58 (1H, d, $J=2.7\text{Hz}$), 6.69 (1H, dd, $J=2.7$ and 8.4Hz), 7.02 (1H, d, $J=8.4\text{Hz}$)

MASS (m/z) : 291 (M^+)

Preparation 17

A suspension of N-tert-butoxycarbonyl-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (2.0 g) in 47% hydrobromic acid (11.8 ml) was refluxed for 2.5 hours. After cooling, the obtained solution was evaporated in vacuo and further evaporated with ethanol twice. The residue was crystallized from diethyl ether and isopropyl alcohol to afford 7-hydroxy-2-methyl-1,2,3,4-tetrahydro-2-naphthylamine hydrobromide.

mp : 280-282°C

IR (Nujol) : 3225 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.26 (3H, s), 1.74-2.01 (2H, m), 2.57-3.00 (4H, m), 6.49 (1H, d, $J=2.5\text{Hz}$), 6.58 (1H, dd, $J=2.5$ and 8.2Hz), 6.92 (1H, d, $J=8.2\text{Hz}$), 8.04 (3H, br s), 9.16 (1H, br s)

Preparation 18

To a solution of 7-hydroxy-2-methyl-1,2,3,4-tetrahydro-2-naphthylamine hydrobromide (1.31 g) in water (20 ml) was added sodium hydrogencarbonate (1.28 g) and tetrahydrofuran (8 ml). To the mixture was added a

solution of benzyloxycarbonyl chloride (0.76 ml) in tetrahydrofuran (4 ml) at 25°C. After stirring for 2 hours, sodium chloride was added to the mixture. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of chloroform and methanol (10:1) as an eluent to afford N-benzyloxycarbonyl-(7-hydroxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (1.59 g) as an oil. This compound was crystallized from a mixture of ethyl acetate (3 ml) and cyclohexane (14.5 ml) to afford a white powder (1.24 g).

mp : 119-121°C

IR (Nujol) : 3340, 1660 cm^{-1}

NMR (CDCl_3 , δ) : 1.46 (3H, s), 1.64-1.82 (1H, m), 2.21-2.45 (1H, m), 2.65-3.02 (4H, m), 4.73 (1H, br s), 5.04 (2H, s), 5.10 (1H, br s), 6.51 (1H, d, $J=2.7\text{Hz}$), 6.63 (1H, dd, $J=2.7$ and 8.2Hz), 6.95 (1H, d, $J=8.2\text{Hz}$), 7.32 (5H, s)

Preparation 19

A mixture of N-benzyloxycarbonyl-(7-hydroxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (1.37 g), potassium carbonate (0.67 g) and ethyl bromoacetate (0.59 ml) in dimethylformamide (14 ml) was stirred at ambient temperature overnight. To the mixture was added cold water (60 ml) and the aqueous layer was decanted twice. The residue was dissolved in diisopropyl ether and the solution was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from petroleum ether to afford N-benzyloxycarbonyl-(7-ethoxycarbonylmethoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (1.66 g) as a powder.

mp : 83.5-84.5°C

IR (Nujol) : 3360, 1750, 1720 cm^{-1}

NMR (CDCl₃, δ) : 1.30 (3H, t, J=7.1Hz),
1.46 (3H, s), 1.62-1.79 (1H, m), 2.25-2.46 (1H,
m), 2.74 (2H, pseudo t, J=7Hz), 2.87 (2H, s),
4.27 (2H, q, J=7.1Hz), 4.57 (2H, s), 4.70 (1H,
s), 5.04 (2H, s), 6.58 (1H, d, J=2.7Hz),
6.70 (1H, dd, J=2.7 and 8.4Hz), 7.00 (1H, d,
J=8.4Hz), 7.32 (5H, s)

Preparation 20

A solution of N-benzyloxycarbonyl-(7-ethoxycarbonyl-methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amine (0.30 g) in a mixture of tetrahydrofuran (1.5 ml) and ethanol (1.5 ml) was hydrogenated at ambient temperature using 10% palladium on carbon (15 mg). After removal of the catalyst, ethyl acetate and saturated sodium hydrogencarbonate solution were added to the solution. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo to afford 7-ethoxycarbonylmethoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthylamine (191 mg) as an oil.

IR (Film) : 3350, 1750, 1730 cm⁻¹

NMR (CDCl₃, δ) : 1.20 (3H, s), 1.30 (3H, t, J=7.1Hz), 1.77 (2H, pseudo t, J=6.8Hz), 2.80-3.10 (6H, m), 4.27 (2H, q, J=7.1Hz), 4.57 (3H, s), 6.59 (1H, d, J=2.7Hz), 6.71 (1H, dd, J=2.7 and 8.4Hz), 7.03 (1H, d, J=8.4Hz)

MASS (m/z) : 263 (M⁺)

Preparation 21

To a suspension of N,O-dimethylhydroxylamine hydrochloride (12.66 g) in dichloromethane (127 ml) was added triethylamine (39.8 ml) at -5°C to 3°C and the whole was stirred for 15 minutes. To the suspension was added a solution of 3-chlorobenzoylchloride (22.72 g) in

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dichloromethane (33 ml) and the whole was stirred for 30 minutes. The mixture was poured into ice water (440 ml) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (100 ml) and the combined organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by distillation under reduced pressure to afford N-methoxy-N-methyl-3-chlorobenzamide (25.53 g).

bp : 106°C/0.3 mmHg

IR (Film) : 1660, 1640 cm^{-1}

NMR (CDCl_3 , δ) : 3.36 (3H, s), 3.55 (3H, s),
7.24-7.73 (4H, m)

MASS (m/z) : 199 (M^+)

15 Preparation 22

To a solution of n-propylmagnesium iodide (7.29 g : prepared from n-propyliodide 6.38 g and magnesium 0.91 g) in diethyl ether (9.3 ml) was added a solution of N-methoxy-N-methyl-3-chlorobenzamide (5.0 g) in diethyl ether (25 ml) at 6-9°C and the whole was stirred overnight. The solution was poured into saturated ammonium chloride solution (75 ml) and the pH of the mixture was adjusted to 1. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of n-hexane and ethyl acetate (20:1) as an eluent to afford 3'-chlorobutyrophenone (2.46 g) as an oil.

IR (Film) : 1690 cm^{-1}

NMR (CDCl_3 , δ) : 1.00 (3H, t, J=7.4Hz), 1.65-1.90 (2H, m), 2.93 (2H, t, J=7.4Hz), 7.33-7.60 (2H, m), 7.79-8.00 (2H, m)

MASS (m/z) : 182 (M^+)

Preparation 23

To a solution of 3'-chlorobutyrophenone (0.50 g) in dimethoxyethane (5 ml) was dropwise added bromine (0.26 ml) at 0°C and the whole was stirred for 30 minutes at ambient temperature. The solution was evaporated in vacuo and water and ethyl acetate were added to the residue. The organic layer was separated, washed with saturated sodium thiosulfate solution and brine, dried over sodium sulfate, and evaporated in vacuo to afford 2-bromo-3'-chlorobutyrophenone (0.72 g) as an oil. This compound was used to the next reaction without further purification.

IR (Film) : 1685 cm^{-1}

NMR (CDCl_3 , δ) : 1.09 (3H, t, $J=7.3\text{Hz}$), 2.00-2.39 (2H, m), 4.99 (1H, dd, $J=6.4$ and 7.7Hz), 7.38-7.64 (2H, m), 7.84-8.03 (2H, m)

Preparation 24

To an ice-cooled solution of (S)-2-benzyloxycarbonyl-amino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene (0.30 g) and methyl iodide (0.24 ml) in N,N-dimethylformamide (7.8 ml) was added sodium hydride (60% dispersion in mineral oil; 78 mg). The mixture was stirred in an ice-bath for 4.5 hours. The reaction mixture was poured into brine, and extracted with ethyl acetate. The extract was washed twice with water and once with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (gradient elution; 5:1 to 4:1 n-hexane-ethyl acetate) which afforded the desired product (0.10 g). Resubjection of some mixed fractions from the chromatography to medium pressure column chromatography (5:1 n-hexane-ethyl acetate as an eluent) gave an additional product (0.090 g), for a total of 0.19 g of (S)-2-(N-benzyloxycarbonyl-N-methyl)amino-7-ethoxy-

carbonylmethoxy-1,2,3,4-tetrahydronaphthalene.

IR (Film) : 3600, 3500, 3350, 1750, 1680 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 1.7-2.1 (2H, m), 2.7-3.0 (4H, m), 2.87 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.2-4.6 (1H, m), 4.57 (2H, s), 5.15 (2H, s), 6.60 (1H, d, $J=2\text{Hz}$), 6.69 (1H, dd, $J=2$ and 8Hz), 6.99 (1H, d, $J=8\text{Hz}$), 7.35 (5H, s)

MASS (m/z) : 397

10 Preparation 25

The following compound was obtained according to a similar manner to that of Preparation 20.

15 (S)-2-Methylamino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene

IR (Nujol) : 3400, 1760 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.87 (1H, br s), 1.9-2.2 (1H, m), 2.3-2.6 (1H, m), 2.76 (3H, s), 2.7-3.0 (2H, m), 3.0-3.5 (3H, m), 4.26 (2H, q, $J=7\text{Hz}$), 4.56 (2H, s), 6.61 (1H, d, $J=2\text{Hz}$), 6.74 (1H, dd, $J=2$ and 8Hz), 7.00 (1H, d, $J=8\text{Hz}$)

MASS (m/z) : 263

Preparation 26

25 To 2-amino-1,1-dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (8.28 g) was added a solution of D-(-)-mandelic acid (6.15 g) in ethanol (114 ml). The mixture was allowed to stand at ambient temperature overnight. The salt was collected and recrystallized
30 twice from ethanol to give a diastereoisomer (3.12 g) with purity of 97% diastereomeric excess by high performance liquid chromatography analysis.

$[\alpha]_D^{23} = -65.7^\circ$ (C=0.545, DMSO)

35 The salt was neutralized with 28% ammonium hydroxide,

and the whole was evaporated twice with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give (S)-2-amino-1,1-dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (1.76 g).

IR (Film) : 3350 cm^{-1}

NMR (CDCl_3 , δ) : 1.23 (3H, s), 1.33 (3H, s), 1.65 (2H, s), 1.6-2.1 (2H, m), 2.7-3.0 (3H, m), 3.78 (3H, s), 6.68 (1H, dd, J=2 and 8Hz), 6.88 (1H, d, J=2Hz), 6.98 (1H, d, J=8Hz)

MASS (m/z) : 205

Preparation 27

The following compound was obtained according to similar manners to those of Preparations 2 and 17.

(S)-2-tert-Butoxycarbonylamino-1,1-dimethyl-7-hydroxy-1,2,3,4-tetrahydronaphthalene

IR (Nujol) : $3600\text{-}3100, 1680\text{ cm}^{-1}$

NMR (CDCl_3 , δ) : 1.22 (3H, s), 1.28 (3H, s), 1.45 (9H, s), 1.7-2.2 (2H, m), 2.78 (2H, t-like, J=ca. 6Hz), 3.7-3.9 (1H, m), 4.60 (1H, br d, J=9Hz), 5.51 (1H, s), 6.62 (1H, dd, J=2 and 8Hz), 6.80 (1H, d, J=2Hz), 6.90 (1H, d, J=8Hz)

MASS (m/z) : 291

Preparation 28

The following compound was obtained according to a similar manner to that of Preparation 19.

(S)-2-tert-Butoxycarbonylamino-1,1-dimethyl-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene

IR (Film) : $3380, 1750, 1700\text{ cm}^{-1}$

NMR (CDCl_3 , δ) : 1.23 (3H, s), 1.30 (3H, s), 1.30 (3H, t, J=7Hz), 1.44 (9H, s), 1.7-2.2 (2H, m),

2.81 (2H, t-like, $J = \text{ca. } 6\text{Hz}$), 3.7-3.9 (1H, m),
4.27 (2H, q, $J = 7\text{Hz}$), 4.5-4.6 (1H, m), 4.59 (2H,
s), 6.66 (1H, dd, $J = 2$ and 8Hz), 6.91 (1H, d,
 $J = 2\text{Hz}$), 6.98 (1H, d, $J = 8\text{Hz}$)

5 MASS (m/z) : 337

Preparation 29

The following compound was obtained according to a
similar manner to that of Preparation 4.

10

(S)-2-Amino-1,1-dimethyl-7-ethoxycarbonylmethoxy-
1,2,3,4-tetrahydronaphthalene hydrochloride

15 NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J = 7\text{Hz}$), 1.23 (3H,
s), 1.35 (3H, s), 1.8-2.1 (2H, m), 2.74 (2H, m),
3.2-3.3 (1H, m), 4.16 (2H, q, $J = 7\text{Hz}$), 4.74 (2H,
s), 6.71 (1H, dd, $J = 2$ and 8Hz), 6.92 (1H, d,
 $J = 2\text{Hz}$), 6.98 (1H, d, $J = 8\text{Hz}$), 8.13 (3H, br s)

Preparation 30

20 To a mixture of 2-benzylamino-7-methoxy-1,2,3,4-
tetrahydronaphthalene hydrochloride (15.1 g),
triethylamine (20.8 ml), and N,N-dimethylformamide (50 ml)
was added methyl chloroformate (5.7 ml). The mixture was
stirred at ambient temperature for 4 hours and then a
25 solution consisting of methyl chloroformate (5.7 ml) and
triethylamine (10.4 ml) in N,N-dimethylformamide (25 ml)
was added. After an additional stirring at ambient
temperature for 4 hours and then at 60°C for 4 hours, the
reaction mixture was diluted with ethyl acetate. The
30 formed precipitate was filtered off, and rinsed several
times with ethyl acetate. The filtrate was concentrated
in vacuo and the residue was taken up in ethyl acetate.
The organic layer was successively washed twice with 3N
hydrochloric acid, once with water and once with brine,
35 dried over anhydrous magnesium sulfate, and concentrated

in vacuo. The residue was purified by column chromatography on silica gel (elution with 4:1 n-hexane-ethyl acetate) to give 2-(N-benzyl-N-methoxycarbonyl)-amino-7-methyl-1,2,3,4-tetrahydronaphthalene (11.9 g).

5 NMR (CDCl₃, δ) : 1.8-2.0 (2H, m), 2.7-3.0 (4H, m),
3.73 (3H, s), 3.74 (3H, s), 4.0-4.8 (1H, br m),
4.51 (2H, br s), 6.52 (1H, d, J=2Hz), 6.66 (1H,
dd, J=2 and 8Hz), 6.95 (1H, d, J=8Hz), 7.2-7.5
(5H, m)

10 MASS (m/z) : 325

Preparation 31

To a solution of 2-(N-benzyl-N-methoxycarbonyl)amino-7-methoxy-1,2,3,4-tetrahydronaphthalene (11.9 g) in
15 1,4-dioxane (119 ml) and water (11.9 ml) was added
2,3-dichloro-5,6-dicyano-1,4-benzoquinone (16.6 g). After
stirring at ambient temperature for 3 hours, the mixture
was filtered and the filtrate was concentrated in vacuo.
The residue was triturated with ethyl acetate, and the
20 precipitate was filtered off. The filtrate was
successively washed with 10% sodium hydroxide, water and
brine, dried over anhydrous sodium sulfate, and
concentrated in vacuo. The residue was purified by column
chromatography on silica gel (elution with 3:1
25 n-hexane-ethyl acetate) to give 2-(N-benzyl-N-methoxy-
carbonyl)amino-7-methoxy-4-oxo-1,2,3,4-
tetrahydronaphthalene (9.8 g).

NMR (CDCl₃, δ) : 2.6-3.5 (4H, m), 3.77 (3H, s), 3.82
(3H, s), 4.3-4.5 (1H, m), 4.57 (2H, br s), 6.63
30 (1H, d, J=2Hz), 6.82 (1H, dd, J=2 and 8Hz),
7.2-7.5 (5H, m), 7.95 (1H, d, J=8Hz)

MASS (m/z) : 339

Preparation 32

35 A mixture of 2-(N-benzyl-N-methoxycarbonyl)amino-7-

methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene (6.9 g),
N-methylanilinium trifluoroacetate (8.9 g),
paraformaldehyde (1.2 g), and tetrahydrofuran (69 ml) was
heated to reflux for 4 hours. After cooling, the reaction
5 mixture was concentrated in vacuo. The residue was
extracted three times with hot ethyl acetate, and the
combined extracts were washed with saturated aqueous
sodium carbonate and brine, dried over anhydrous magnesium
sulfate, and concentrated in vacuo. Solvent removal was
10 followed by column chromatography on silica gel (elution
with 4:1 n-hexane-ethyl acetate) to give crude
2-(N-benzyl-N-methoxycarbonyl)amino-7-methoxy-3-methylene-
4-oxo-1,2,3,4-tetrahydronaphthalene.

IR (Nujol) : 1700, 1670, 1600 cm^{-1}
15 NMR (CDCl_3 , δ) : 2.80 (1H, dd, J=5 and 15Hz), 3.19
(1H, dd, J=12 and 15Hz), 3.76 (1H, d, J=16Hz),
3.77 (3H, s), 3.80 (3H, s), 3.85 (1H, d,
J=16Hz), 4.6-5.0 (1H, m), 5.42 (1H, br s), 6.51
(2H, br s), 6.84 (1H, dd, J=2 and 8Hz), 7.1-7.4
20 (5H, m), 8.03 (1H, d, J=8Hz)
MASS (m/z) : 351

The crude product was dissolved in tetrahydrofuran (6
ml) and water (6 ml). To this solution was added 10%
25 palladium on carbon (0.6 g). The slurry was stirred under
an atmosphere of hydrogen for half an hour. The catalyst
was filtered off, and rinsed with tetrahydrofuran. The
filtrate was concentrated in vacuo to give cis-2-(N-
benzyl-N-methoxycarbonyl)amino-7-methoxy-3-methyl-4-oxo-
30 1,2,3,4-tetrahydronaphthalene.

NMR (CDCl_3 , δ) : 1.26 (3H, d, J=7Hz), 2.8-3.2 (3H,
m), 3.69 (3H, s), 3.74 (3H, s), 3.7-3.9 (1H, m),
4.7-5.2 (2H, m), 6.7-7.0 (2H, m), 7.0-7.4 (5H,
m), 7.97 (1H, d, J=8Hz)
35 MASS (m/z) : 353

The product was dissolved in boron trifluoride etherate (20 ml) and treated with triethylsilane (12.9 ml). After stirring at ambient temperature for 12 hours, the reaction mixture was poured into water, and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 8:1 n-hexane-ethyl acetate) to give a mixture of cis- and trans-2-(N-benzyl-N-methoxycarbonyl)-amino-7-methoxy-3-methyl-1,2,3,4-tetrahydronaphthalene (1.5 g).

IR (Film) : 1690 cm^{-1}

NMR (CDCl_3 , δ) : 0.8-1.1 (6H, m), 2.0-3.2 (10H, m), 3.7-3.8 (12H, m), 3.8-4.2 (2H, m), 4.2-4.4 (2H, m), 4.5-4.8 (2H, m), 6.4-6.6 (2H, m), 6.6-6.8 (2H, m), 6.8-7.0 (2H, m), 7.1-7.5 (10H, m)

MASS (m/z) : 339

Preparation 33

The following compound was obtained according to a similar manner to that of Preparation 17.

cis- and trans-2-Benzylamino-7-hydroxy-3-methyl-1,2,3,4-tetrahydronaphthalene

IR (Film) : $3600\text{--}2200\text{ cm}^{-1}$

NMR (CDCl_3 , δ) : 0.98 (3H, d, $J=7\text{Hz}$), 1.07 (3H, d, $J=7\text{Hz}$), 1.4-3.2 (16H, m), 3.7-4.1 (4H, m), 6.5-6.7 (4H, m), 6.91 (2H, d, $J=8\text{Hz}$), 7.2-7.6 (16H, m)

MASS (m/z) : 267

Preparation 34

The following compounds were obtained by subjecting the mixture of cis- and trans-compounds, which was

prepared according to a similar manner to that of Preparation 19, to silica gel column chromatography.

- 1) cis-2-Benzylamino-7-ethoxycarbonylmethoxy-3-methyl-
5 1,2,3,4-tetrahydronaphthalene
IR (Film) : 3350, 1750 cm^{-1}
NMR (CDCl_3 , δ) : 0.96 (3H, d, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 1.4-2.1 (1H, m), 2.1-2.4 (1H, m), 2.56 (1H, m), 2.6-3.1 (4H, m), 3.83 (1H, d, $J=13\text{Hz}$),
10 3.89 (1H, d, $J=13\text{Hz}$), 4.26 (2H, q, $J=7\text{Hz}$), 4.57 (2H, s), 6.61 (1H, d, $J=2\text{Hz}$), 6.68 (1H, dd, $J=2$ and 8Hz), 6.97 (1H, d, $J=8\text{Hz}$), 7.2-7.5 (5H, m)
MASS (m/z) : 353
- 15 2) trans-2-Benzylamino-7-ethoxycarbonylmethoxy-3-methyl-
1,2,3,4-tetrahydronaphthalene
IR (Film) : 3350, 1750 cm^{-1}
NMR (CDCl_3 , δ) : 1.09 (3H, d, $J=7\text{Hz}$), 1.30 (3H, t, $J=7\text{Hz}$), 1.8-2.2 (1H, m), 2.40 (1H, m), 2.6-3.0 (4H, m), 3.0-3.2 (1H, m), 3.84 (1H, d, $J=13\text{Hz}$),
20 3.99 (1H, d, $J=13\text{Hz}$), 4.26 (2H, q, $J=7\text{Hz}$), 4.56 (2H, s), 6.6-6.8 (2H, m), 6.96 (1H, d, $J=8\text{Hz}$), 7.1-7.6 (5H, m)
MASS (m/z) : 353

25

Example 1

A solution of 2,2"-oxybis[3'-chloro-2,4'-
dihydroxyacetophenone] (47 mg), (S)-2-amino-7-
ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene
30 hydrochloride (57 mg) and triethylamine (24 mg) in ethanol (1 ml) was stirred at ambient temperature for 50 minutes and cooled with ice water. Sodium borohydride (37.5 mg) was added to the mixture, and the resulting mixture was stirred under ice cooling for 15 minutes and at ambient
35 temperature overnight. The reaction mixture was diluted

with water and extracted twice with dichloromethane. The extracts were combined, dried over magnesium sulfate, and filtered. The filtrate was purified by two times column chromatography using chloroform, ethanol and methanol to give an oil, which was converted to oxalate to give a pale yellow powder of a mixture of (1R,2'S)- and (1S,2'S)-1-(3-chloro-4-hydroxyphenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol oxalate (12 mg).

mp : 105°C (dec.)
IR (Nujol) : 3350, 2750-2350, 1745, 1615, 1205 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.21 (6H, t, J=7Hz), 1.65 (2H, m), 2.1 (2H, m), 2.6-3.5 (14H, m), 4.16 (4H, quartet, J=7Hz), 4.71 (6H, m), 6.65 (4H, m), 7.0 (4H, m), 7.15 (2H, m), 7.35 (2H, m)

Example 2

A mixture of trans-2-amino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthol hydrochloride (0.20 g), (R)-3-chlorostyrene oxide (0.11 g), triethylamine (0.10 ml), and ethanol (1.3 ml) was refluxed for 4 hours with stirring. An additional amount of (R)-3-chlorostyrene oxide (0.054 g) in ethanol (1.5 ml) was added, and stirring was continued for an additional 4 hours under reflux. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (eluent:chloroform-methanol = 20:1) afforded a mixture of (1R,1'R,2'R)- and (1R,1'S,2'S)-1-(3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol (0.074 g).

The obtained compound (0.074 g) was treated with 5N hydrogen chloride in ethanol to afford a mixture of (1R,1'R,2'R)- and (1R,1'S,2'S)-1-(3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1-hydroxy-1,2,3,4-tetrahydro-2-

naphthyl)amino]ethanol hydrochloride.

mp : 122-127°C

IR (Nujol) : 3300, 3250, 1740, 1720 cm⁻¹

5 NMR (DMSO-d₆, δ) : 1.21 (6H, t, J=7Hz), 1.7-2.0 (2H, m), 2.2-2.4 (2H, m), 2.7-2.9 (4H, m), 3.1-3.6 (6H, m), 4.16 (4H, q, J=7Hz), 4.74 (4H, s), 4.7-4.9 (2H, m), 5.0-5.2 (2H, m), 6.2-6.4 (4H, m), 6.79 (2H, dd, J=2 and 8Hz), 7.0-7.1 (4H, m), 7.4-7.6 (8H, m), 8.4-9.5 (4H, m)

10 MASS (m/z) : 422 and 420 (M⁺(free)+1)

Example 3

(S)-2-Amino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride (2.11 g) was converted to a free amine by treatment with sodium bicarbonate aqueous solution. A solution of the obtained free amine and (+)-[3-chloro-4-(2-methoxyethoxymethoxy)phenyl]oxirane (1.91 g) in ethanol (20 ml) was refluxed for 9 hours and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol as an eluent to give an oil of (-)-1-[3-chloro-4-(2-methoxyethoxymethoxy)-phenyl]-2-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl]amino]ethanol (1.65 g) (a single stereoisomer).

25 $[\alpha]_D^{20.0} = -45.38^\circ$ (C=0.52, MeOH)

IR (Film) : 3400-3300, 1755, 1735, 1235, 1195, 1160, 1125, 1100, 1070 cm⁻¹

30 NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 1.62 (1H, m), 2.03 (1H, m), 2.43 (1H, broad), 2.55-3.1 (7H, m), 3.37 (3H, s), 3.56 (2H, m), 3.87 (2H, m), 4.27 (2H, quartet, J=7Hz), 4.58 (2H, s), 4.64 (1H, dd, J=3.5 and 9Hz), 5.33 (2H, s), 6.61 (1H, d, J=2.5Hz), 6.70 (1H, dd, J=2.5 and 8.5Hz), 35 7.00 (1H, d, J=8.5Hz), 7.20 (2H, s), 7.41 (1H, s)

Example 4

A solution of (-)-1-[3-chloro-4-(2-methoxyethoxy-methoxy)phenyl]-2-[[{(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl}amino]ethanol (a single stereoisomer) (1.62 g) in 0.2M methanesulfonic acid ethanolic solution (24.5 ml) was heated at 50°C for 6 hours, concentrated in vacuo, and partitioned between ethyl acetate and sodium bicarbonate aqueous solution. The organic layer was separated, and the aqueous layer was further extracted twice with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using methylene chloride and methanol as an eluent to give an oil of (-)-1-(3-chloro-4-hydroxyphenyl)-2-[[{(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl}amino]ethanol.

The obtained oil was treated with 4N hydrogen chloride in ethyl acetate and crystallized from diethyl ether to give a colourless powder of (-)-1-(3-chloro-4-hydroxyphenyl)-2-[[{(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl}amino]ethanol hydrochloride (0.95 g) (a single stereoisomer).

$$[\alpha]_D^{22.4} = -82.49^\circ \text{ (C=0.48, MeOH)}$$

IR (Nujol) : 3400-3100, 2800-2300, 1735, 1210 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (3H, t, J=7Hz), 1.8 (1H, m), 2.3 (1H, m), 2.6-3.6 (7H, m), 4.16 (2H, quartet, J=7Hz), 4.72 (2H, s), 4.95 (1H, m), 6.17 (1H, d, J=4Hz), 6.66 (1H, d, J=2.5Hz), 6.71 (1H, dd, J=2.5 and 8.5Hz), 7.01 (2H, d, J=8.5Hz), 7.19 (1H, dd, J=2 and 8.5Hz), 7.39 (1H, d, J=2Hz), 8.85 (1H, broad), 9.3 (1H, broad)

MASS (m/z) : 422 and 420 ($M^+(\text{free})+1$), 402, 262, 233

Analysis Calcd. for $\text{C}_{22}\text{H}_{26}\text{ClNO}_5 \cdot \text{HCl}$

C 57.90, H 5.96, N 3.07

Found : C 57.56, H 6.10, N 3.06

Example 5

The following compounds were obtained according to a similar manner to that of Example 1.

- 5 1) (1R,2'S)- and (1S,2'S)-1-(4-Benzyloxy-3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride
mp : 109-119°C
IR (Nujol) : 3320, 2750, 2350, 1740, 1255, 1200 cm⁻¹
10 NMR (DMSO-d₆, δ) : 1.21 (6H, t, J=7Hz), 1.78 (2H, m), 2.31 (2H, m) 2.78 (6H, m), 3.18 (6H, m), 3.45 (2H, m), 4.15 (4H, quartet, J=7Hz), 4.72 (4H, s), 4.96 (2H, m), 5.24 (4H, s), 6.25 (2H, m), 6.66 (2H, m), 6.74 (2H, m), 7.02 (2H, d, J=8.5Hz), 7.2-7.55 (16H, m), 8.86 (2H, br), 9.36 (2H, br)
15 FAB-MASS (m/z) : 510 (M⁺(free)+1), 492, 262, 233
- 20 2) (1R,2'R)- and (1S,2'R)-1-(4-Benzyloxy-3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride
mp : 117-123°C
IR (Nujol) : 3370, 2750-2350, 1720, 1255, 1200 cm⁻¹
25 NMR (DMSO-d₆, δ) : 1.21 (6H, t, J=7Hz), 1.8 (2H, m), 2.3 (2H, m), 2.77 (6H, m), 3.18 (6H, m), 3.45 (2H, m), 4.16 (4H, quartet, J=7Hz), 4.72 (4H, s), 4.94 (2H, m), 5.24 (14H, s), 6.24 (2H, m), 6.69 (2H, m), 6.74 (2H, m), 7.02 (2H, d, J=8.5Hz), 7.2-7.55 (16H, m), 8.85 (2H, br), 9.35 (2H, br)
30 (2H, br)
- 35 3) (1R,2'S)- and (1S,2'S)-1-(3-Chloro-4-methoxyphenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride
mp : 73-98°C

IR (Nujol) : 3300, 1745, 1255, 1200 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.21 (6H, t, $J=7\text{Hz}$), 1.78 (2H, m),
2.30 (2H, m), 2.78 (6H, m), 3.18 (6H, m), 3.45
(2H, m), 3.86 (6H, s), 4.16 (4H, quartet, $J=7\text{Hz}$),
4.72 (4H, s), 4.96 (2H, m), 6.25 (2H, m),
6.65-6.75 (4H, m), 7.02 (2H, d, $J=8\text{Hz}$), 7.18 (2H,
d, $J=8.5\text{Hz}$), 7.37 (2H, dd, $J=8.5$ and 2Hz), 7.50
(2H, d, $J=2\text{Hz}$), 8.85 (2H, br), 9.35 (2H, br)

10 4) (1R,2'S)- and (1S,2'S)-1-(3-Chloro-4-methylsulfonyl-
phenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-
tetrahydro-2-naphthyl)amino]ethanol hydrochloride
mp : 214-220°C (dec.)

15 IR (Nujol) : 3600-3300, 3230, 2750-2350, 1750, 1320,
1200, 1150 cm^{-1}

20 NMR (DMSO-d_6 , δ) : 1.21 (6H, t, $J=7\text{Hz}$), 1.79 (2H,
m), 2.31 (2H, m), 2.78 (6H, m), 3.05 (6H, s),
3.20 (6H, m), 3.45 (2H, m), 4.16 (4H, quartet,
 $J=7\text{Hz}$), 4.72 (4H, s), 5.04 (2H, m), 6.36 (2H,
m), 6.65-6.75 (4H, m), 7.02 (2H, d, $J=8.5\text{Hz}$),
7.35-7.6 (6H, m), 8.93 (2H, br), 9.49 (4H, br)

25 5) (1R,2'S)- and (1S,2'S)-2-[(7-Ethoxycarbonylmethoxy-
1,2,3,4-tetrahydro-2-naphthyl)amino]-1-(3-
phenoxyphenyl)ethanol hydrochloride

mp : 55-56°C

IR (Film) : 3320, 2800-2300, 1745, 1240, 1205 cm^{-1}

30 NMR (DMSO-d_6 , δ) : 1.21 (6H, t, $J=7\text{Hz}$), 1.78 (2H,
m), 2.29 (2H, m), 2.55-3.6 (14H, m), 4.16 (4H,
quartet, $J=7\text{Hz}$), 4.72 (4H, s), 5.02 (2H, m),
6.28 (2H, m), 6.65-6.75 (4H, m), 6.9-7.25 (14H,
m), 7.35-7.5 (6H, m), 8.89 (2H, br), 9.43 (2H,
br)

35 6) (1R,2'S)- and (1S,2'S)-1-(4-Amino-3,5-dichlorophenyl-

2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride

IR (Film) : 3310, 1745 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 1.21 (6H, t, $J=7.1\text{Hz}$), 1.60-1.95 (2H, m), 2.21-2.42 (2H, m), 2.58-3.58 (14H, m), 4.16 (4H, q, $J=7.1\text{Hz}$), 4.72 (4H, s), 4.80-4.95 (2H, m), 6.60-6.76 (4H, m), 7.02 (2H, d, $J=8.4\text{Hz}$), 7.31 (4H, m)

10 7) (1R,2'S)- and (1S,2'S)-1-(3-Chloro-4-fluorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride

mp : 181-184°C

IR (Nujol) : 3300, 2700-2300, 1760 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 1.20 (6H, t, $J=7\text{Hz}$), 1.6-2.0 (2H, m), 2.2-3.6 (14H, m), 4.15 (4H, q, $J=7\text{Hz}$), 4.72 (4H, s), 5.0-5.2 (2H, m), 6.3-6.5 (2H, br s), 6.6-6.8 (6H, m), 6.9-7.1 (2H, m), 7.4-7.5 (4H, m), 7.6-7.7 (2H, m), 8.8-9.2 (2H, m), 9.4-9.8 (2H, m)

20 FAB-MASS (m/z) : 424 ($\text{M}^+(\text{free})+3$), 422 ($\text{M}^+(\text{free})+1$)

25 8) (1R,2'S)- and (1S,2'S)-2-[7-(Ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]-1-(3-methoxyphenyl)ethanol hydrochloride

mp : 152-154°C

IR (Nujol) : 3330, 1745, 1610 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 1.21 (6H, t, $J=7\text{Hz}$), 1.65-1.9 (2H, m), 2.2-3.6 (16H, m), 3.78 (6H, s), 4.15 (4H, q, $J=7\text{Hz}$), 4.72 (4H, s), 4.95-5.1 (2H, m), 6.2-6.3 (2H, m), 6.6-6.75 (4H, m), 6.85-7.05 (8H, m), 7.25-7.4 (2H, m), 8.7-9.0 (2H, m), 9.2-9.5 (2H, m)

35 9) (1R,2'S)- and (1S,2'S)-2-[7-(Ethoxycarbonylmethoxy-

1,2,3,4-tetrahydro-2-naphthyl)amino]-1-(3-nitrophenyl)ethanol hydrochloride

mp : 177-179°C

IR (Nujol) : 3300 1730, 1620 cm⁻¹

NMR (DMSO-d₆, δ) : 1.21 (6H, t, J=7Hz), 1.65-1.95 (2H, m), 2.25-3.6 (16H, m), 4.15 (4H, q, J=7Hz), 4.72 (4H, s), 5.15-5.30 (2H, m), 6.5-6.6 (2H, m), 6.6-6.8 (4H, m), 6.95-7.1 (2H, m), 7.7-7.8 (2H, m), 7.9-8.0 (2H, m), 8.15-8.3 (2H, m), 8.35 (2H, s), 8.9-9.1 (2H, m), 9.3-9.5 (2H, m)

MASS (m/z) : 415 (M⁺(free)+1)

10) (1R,2'S)- and (1S,2'S)-1-(3-Cyanophenyl)-2-[7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)-amino]ethanol hydrochloride

mp : 171-174°C

IR (Nujol) : 3300, 2220, 1720, 1605 cm⁻¹

NMR (DMSO-d₆, δ) : 1.21 (6H, t, J=7Hz), 1.6-1.9 (2H, m), 2.2-3.6 (16H, m), 4.15 (4H, q, J=7Hz), 4.72 (4H, s), 5.05-5.2 (2H, m), 6.4-6.5 (2H, m), 6.6-6.8 (4H, m), 6.95-7.1 (2H, m), 7.6-7.75 (2H, m), 7.75-7.85 (4H, m), 7.91 (2H, s), 8.8-9.1 (2H, m), 9.3-9.6 (2H, m)

Example 6

The following compounds were obtained by reacting the compounds, which were prepared according to a similar manner to that of Example 3, with the corresponding acid.

1) (-)-1-(4-Benzoyloxy-3-chlorophenyl)-2-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride (a single stereoisomer)

mp : 61-69°C

[α]_D^{31.2} = -67.54° (C=0.53, MeOH)

IR (Nujol) : 3350-3150, 2750-2350, 1740, 1255, 1200 cm⁻¹

5 NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J=7\text{Hz}$), 1.78 (1H, m), 2.27 (1H, m), 2.78 (3H, m), 3.18 (3H, m), 3.45 (1H, m), 4.15 (2H, quartet, $J=7\text{Hz}$), 4.71 (2H, s), 4.98 (1H, m), 5.24 (2H, s), 6.25 (1H, d, $J=4\text{Hz}$), 6.66 (1H, d, $J=2\text{Hz}$), 6.72 (1H, dd, $J=8.5$ and 2Hz), 7.02 (1H, d, $J=8.5\text{Hz}$), 7.2-7.55 (8H, m), 8.92 (1H, br), 9.88 (1H, br)

10 2) (+)-1-(4-Benzoyloxy-3-chlorophenyl)-2-[(2R)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl]amino]ethanol hydrochloride (a single stereoisomer)

mp : 135-137.5°C

$[\alpha]_D^{31.6} = 25.88^\circ$ ($C=0.255$, MeOH)

IR (Nujol) : 3340, 2750-2250, 1720, 1255, 1205 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J=7\text{Hz}$), 1.71 (1H, m), 2.30 (1H, m), 2.77 (3H, m), 3.15 (3H, m), 3.44 (1H, m), 4.16 (2H, quartet, $J=7\text{Hz}$), 4.72 (2H, s), 4.95 (1H, m), 5.24 (2H, s), 6.23 (1H, d, $J=4\text{Hz}$), 6.65-6.75 (2H, m), 7.02 (1H, d, $J=8.5\text{Hz}$), 7.2-7.55 (8H, m), 8.83 (1H, br), 9.35 (1H, br)

25 3) (-)-1-[3-Chloro-4-(2-methoxyethoxymethoxy)phenyl]-2-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl]amino]ethanol oxalate (a single stereoisomer)

mp : 68-70°C

$[\alpha]_D^{23.6} = -72.80^\circ$ ($C=0.25$, MeOH)

30 IR (Film) : 3440, 3400, 2800-2300, 1740, 1605, 1230 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J=7\text{Hz}$), 1.74 (1H, m), 2.19 (1H, m), 2.77 (3H, m), 3.12 (3H, m), 3.22 (3H, s), 3.44 (1H, m), 3.47 (2H, m), 3.75 (2H, m), 4.15 (2H, quartet, $J=7\text{Hz}$), 4.71 (2H, s), 4.91 (1H, br d, $J=8\text{Hz}$), 5.35 (2H, s), 5.8

(4H, br), 6.6-6.75 (2H, m), 7.02 (1H, d, J=8.5Hz), 7.2-7.4 (2H, m), 7.51 (1H, d, J=2Hz)

- 5 4) (1R,2'S)- and (1S,2'S)-1-(5-Chloro-2-fluorophenyl-2-
[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride

mp : 150-152°C

IR (Nujol) : 3280, 2750-2350, 1740 cm⁻¹

10 NMR (DMSO-d₆, δ) : 1.28 (6H, t, J=7Hz), 1.6-2.0 (2H, m), 2.2-3.6 (14H, m), 4.15 (4H, q, J=7Hz), 4.72 (4H, s), 5.2-5.4 (2H, m), 6.4-6.5 (2H, m), 6.6-6.8 (4H, m), 6.9-7.1 (2H, m), 7.2-7.7 (6H, m), 8.8-9.2 (2H, m), 9.5-9.9 (2H, m)

15 FAB-MASS (m/z) : 424 (M⁺(free)+3), 422 (M⁺(free)+1)

- 5) (1R,2'S)- and (1S,2'S)-2-[(7-Ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]-1-(3-trifluoromethoxy)ethanol hydrochloride

mp : 163-164°C

20 IR (Nujol) : 3300, 2700-2400, 1740 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.20 (6H, t, J=7Hz), 1.6-2.0 (2H, m), 2.2-3.6 (14H, m), 4.15 (4H, q, J=7Hz), 4.71 (4H, s), 5.0-5.2 (2H, m), 6.4-6.5 (2H, m), 6.6-6.8 (4H, m), 6.9-7.1 (2H, m), 7.3-7.6 (8H, m), 8.8-9.2 (2H, m), 9.3-9.5 (2H, m)

FAB-MASS (m/z) : 456 (M⁺(free)+3), 454 (M⁺(free)+1)

- 30 6) (1R,2'S)-2-[(6-Chloro-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]-1-(3-chlorophenyl)ethanol hydrochloride

mp : 97-101°C

IR (Nujol) : 3300, 3100-2000, 1740, 1720 cm⁻¹

35 NMR (DMSO-d₆, δ) : 1.21 (3H, t, J=7Hz), 1.6-2.0 (1H, m), 2.2-2.5 (1H, m), 2.6-3.8 (5H, m), 4.16 (2H, q, J=7Hz), 4.84 (2H, s), 5.0-5.2 (1H, m),

6.3-6.5 (1H, m), 6.78 (1H, s), 7.20 (1H, s),
7.3-7.6 (4H, m), 8.8-9.2 (1H, m), 9.4-9.8 (1H,
m)

FAB-MASS (m/z) : 442 ($M^+ + 5 - HCl$), 440 ($M^+ + 3 - HCl$),
438 ($M^+ + 1 - HCl$)

5

7) (1R,2'S)-1-(3-Chlorophenyl)-2-[[N-(7-ethoxycarbonyl-
methoxy-1,2,3,4-tetrahydro-2-naphthyl)-N-methyl]-
amino]ethanol hydrochloride

10

NMR (DMSO- d_6 , δ) : 1.30 (3H, t, $J=7Hz$), 1.5-2.1 (4H,
m), 2.1-4.0 (8H, m), 4.1-4.4 (2H, m), 4.58 (2H,
s), 5.0-5.8 (2H, m), 6.4-6.9 (2H, m), 6.9-7.1
(1H, m), 7.1-7.6 (4H, m), 11.0-12.0 (1H, m)

15

8) (1R,2'S)-1-(3-Chlorophenyl)-2-[(1,1-dimethyl-7-
ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-
naphthyl)amino]ethanol hydrochloride

20

NMR (DMSO- d_6 , δ) : 1.21 (3H, t, $J=7Hz$), 1.34 (3H,
s), 1.51 (3H, s), 1.7-2.0 (1H, m), 2.1-2.4 (1H,
m), 2.6-3.0 (2H, m), 3.1-3.7 (3H, m), 4.16 (2H,
q, $J=7Hz$), 4.75 (2H, s), 5.0-5.2 (1H, m), 6.43
(1H, d, $J=4Hz$), 6.71 (1H, dd, $J=2$ and $8Hz$),
6.9-7.1 (2H, m), 7.3-7.6 (4H, m), 8.0-8.4 (1H,
m), 9.1-9.5 (1H, m)

25

MASS (m/z) : 433 ($M^+ + 2 - HCl$), 431 ($M^+ - HCl$)

Example 7

(-)-1-(4-Benzoyloxy-3-chlorophenyl)-2-[[{(2S)-7-ethoxy-
carbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl}amino]-
ethanol hydrochloride (a single stereoisomer) (5.32 g) was
catalytically hydrogenated at ambient temperature in
ethanol (400 ml) using 10% palladium on carbon. After
removal of the catalyst, the solution was evaporated in
vacuo. The residue was purified by silica gel column
chromatography using a mixture of dichloromethane and

35

methanol as an eluent, treated with 4N hydrogen chloride in ethyl acetate, and crystallized from diethyl ether. The obtained powder was triturated with ethyl acetate, a mixture of ethyl acetate and ethanol, and ethyl acetate, successively to afford (-)-1-(3-chloro-4-hydroxyphenyl)-2-
5 [((2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride (a single stereoisomer) (2.38 g) as a colorless powder.

mp : 137-142°C

10 $[\alpha]_D^{22.4} = -82.49^\circ$ (C=0.48, MeOH)

IR (Nujol) : 3400-3100, 2800-2300, 1735, 1210 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (3H, t, J=7Hz), 1.8 (1H, m),
2.3 (1H, m), 2.6-3.6 (7H, m), 4.16 (2H, quartet, J=7Hz), 4.72 (2H, s), 4.95 (1H, m), 6.17 (1H, d, J=4Hz),
15 6.66 (1H, d, J=2.5Hz), 6.71 (1H, dd, J=2.5 and 8.5Hz), 7.01 (2H, d, J=8.5Hz), 7.19 (1H, dd, J=2 and 8.5Hz), 7.39 (1H, d, J=2Hz), 8.85 (1H, br), 9.3 (1H, br)

20 MASS (m/z) : 422 and 420 ($M^+(\text{free})+1$), 402, 262, 233

Example 8

The following compounds were obtained according to a similar manner to that of Example 7.

- 25 1) (1R,2'S)- and (1S,2'S)-1-(3-Chloro-4-hydroxyphenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride

mp : 168-171°C (dec.)

30 IR (Nujol) : 3500, 3330, 3200, 3120, 2800-2300, 1750, 1220, 1200 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (6H, t, J=7Hz), 1.78 (2H, m), 2.31 (2H, m), 2.78 (6H, m), 3.15 (6H, m), 3.4 (2H, m), 4.16 (4H, quartet, J=7Hz), 4.72 (4H, s), 4.93 (2H, m), 6.17 (2H, br s),
35 6.65-6.75 (4H, m), 7.02 (4H, d, J=8.5Hz), 7.19

(2H, dd, J=8.5 and 2Hz), 7.89 (2H, d, J=2Hz),
8.85 (2H, br), 9.90 (2H, br), 10.81 (2H, s)
FAB-MASS (m/z) : 422 and 420 (M^+ (free)+1), 402, 262,
233

5

- 2) (1R,2'S)- and (1S,2'S)-1-(3-Chloro-4-hydroxyphenyl)-
2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-
naphthyl)amino]ethanol oxalate

mp : 105°C (dec.)

10

IR (Nujol) : 3350, 2750-2350, 1745, 1615, 1205 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (6H, t, J=7Hz), 1.65 (2H,
m), 2.1 (2H, m), 2.6-3.5 (14H, m), 4.16 (4H,
quartet, J=7Hz), 4.71 (6H, m), 6.65 (4H, m), 7.0
(4H, m), 7.15 (2H, m), 7.35 (2H, m)

15

FAB-MASS (m/z) : 422 and 420 (M^+ (free)+1), 402, 262,
233

- 3) (1R,2'R)- and (1S,2'R)-1-(3-Chloro-4-hydroxyphenyl)-
2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-
naphthyl)amino]ethanol hydrochloride

20

mp : 156-169°C

IR (Nujol) : 3500, 3330, 3200, 3120, 2750-2300,
1745, 1215, 1200 cm^{-1}

25

NMR (DMSO- d_6 , δ) : 1.21 (6H, t, J=7Hz), 1.78 (2H,
m), 2.30 (2H, m), 2.78 (6H, m), 3.15 (6H, m),
3.4 (2H, m), 4.16 (4H, quartet, J=7Hz), 4.72
(4H, s), 4.93 (2H, m), 6.17 (2H, br s),
6.65-6.75 (4H, m), 7.02 (4H, d, J=8.5Hz), 7.19
(2H, dd, J=8.5 and 2Hz), 7.89 (2H, d, J=2Hz),
8.85 (2H, br), 9.90 (2H, br), 10.81 (2H, s)

30

- 4) (+)-1-(3-Chloro-4-hydroxyphenyl)-2-[(2R)-7-
ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-
naphthyl]amino]ethanol hydrochloride (a single
stereoisomer)

35

mp : 147-150°C (dec.)

$[\alpha]_D^{28.8} = 31.51^\circ$ (C=0.165, MeOH)

IR (Nujol) : 3650-3100, 1735, 1215, 1200 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 1.21 (3H, t, J=7Hz), 1.72 (1H, m), 2.30 (1H, m), 2.6-3.0 (3H, m), 3.14 (3H, m), 3.40 (1H, m), 4.16 (2H, quartet, J=7Hz), 4.72 (2H, s), 4.92 (1H, m), 6.15 (1H, br s), 6.65-6.75 (2H, m), 7.01 (2H, d, J=8.5Hz), 7.19 (1H, dd, J=8.5 and 2Hz), 7.39 (1H, d, J=2Hz), 10 8.80 (1H, br), 9.39 (1H, br), 10.29 (1H, s)

Example 9

15 A mixture of (1R,2'S)- and (1S,2'S)-1-(4-benzyloxy-3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol hydrochloride (55 mg), ammonium formate (19 mg), and 10% palladium on carbon (10 mg) in refluxing ethanol (3 ml) was stirred for 1.5 hours. After filtration, the mixture was evaporated in vacuo and partitioned between ethyl acetate and sodium 20 hydrogencarbonate aqueous solution. The organic layer was washed with brine, dried, evaporated in vacuo, and chromatographed over silica gel using a mixture of dichloromethane and methanol as an eluent. The obtained oil was converted to hydrochloride in a usual manner and 25 the hydrochloride was crystallized from diethyl ether to afford a mixture of (1R,2'S)- and (1S,2'S)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)-amino]-1-(4-hydroxyphenyl)ethanol hydrochloride (29 mg) as a pale yellow powder.

30 mp : 64-80°C

IR (Nujol) : 3600-3120, 2700-2050, 1735, 1215, 1200 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 1.21 (6H, t, J=7Hz), 1.75 (2H, m), 2.3 (2H, m), 2.77 (6H, m), 3.15 (6H, m), 3.59 (2H, m), 4.16 (4H, quartet, J=7Hz), 4.72

(4H, s), 4.95 (2H, m), 6.65-7.25 (14H, m), 8.2
(2H, br s), 8.8 (2H, br), 9.2 (2H, br), 9.5 (2H,
br)

FAB-MASS (m/z) : 386 (M^+ (free)+1), 368, 262, 233

5

Example 10

A solution of (-)-1-(3-chloro-4-hydroxyphenyl)-2-
[[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-
naphthyl]amino]ethanol hydrochloride (a single
10 stereoisomer) (240 mg) and 0.1 N sodium hydroxide aqueous
solution (25.6 ml) in ethanol (24 ml) was stirred in a
nitrogen atmosphere at ambient temperature for 1 hour,
neutralized with 0.1N hydrochloric acid, and concentrated
in vacuo. The residue was triturated with a mixture of
15 diethyl ether and water to afford a powder, which was
converted to oxalate in a usual manner. The oxalate was
crystallized from ethyl acetate and washed with diethyl
ether and isopropanol to afford (-)-2-[[[(2S)-7-
carboxymethoxy-1,2,3,4-tetrahydro-2-naphthyl]amino]-1-
20 (3-chloro-4-hydroxyphenyl)ethanol oxalate (a single
stereoisomer) (68 mg) as a colorless powder.

mp : 108°C (dec.)

NMR (DMSO- d_6 , δ) : 1.72 (1H, m), 2.16 (1H, m), 2.74
(3H, m), 3.10 (3H, m), 3.36 (1H, m), 4.52 (2H,
25 s), 4.85 (1H, m), 6.5 (6H, br), 6.55-7.4 (6H, m)

Example 11

The following compounds were obtained according to
similar manners to those of Preparation 20 and Example 3.

30

1) (1R,2'R,3'S)- and (1R,2'S,3'R)-1-(3-Chlorophenyl)-
2-[(7-ethoxycarbonylmethoxy-3-methyl-1,2,3,4-
tetrahydro-2-naphthyl)amino]ethanol hydrochloride
IR (Film) : 3300, 3100-2300, 1730 cm^{-1}

35

NMR (CDCl_3 , δ) : 1.18 (6H, br d, $J=5\text{Hz}$), 1.30 (6H,

5 t, J=7Hz), 1.4-2.4 (4H, m), 2.6-2.9 (4H, m),
2.9-3.8 (10H, m), 4.26 (4H, q, J=7Hz), 4.49 (2H,
s), 4.52 (2H, s), 5.4-5.7 (2H, m), 6.5-6.6 (2H,
m), 6.6-6.8 (2H, m), 6.97 (2H, d, J=8Hz),
7.2-7.5 (6H, m), 7.5-7.6 (2H, m), 8.1-8.4 (1H,
m), 8.4-8.7 (1H, m), 10.0-10.2 (1H, m),
10.2-10.6 (1H, m)

FAB-MASS (m/z) : 420 ($MH^+ + 2-HCl$), 418 ($MH^+ - HCl$)

10 2) (1R,2'R,3'R)- and (1R,2'S,3'S)-1-(3-Chlorophenyl)-2-
[(7-ethoxycarbonylmethoxy-3-methyl-1,2,3,4-
tetrahydro-2-naphthyl)amino]ethanol hydrochloride
IR (Film) : 3250, 3100-2300, 1730 cm^{-1}

15 NMR ($CDCl_3$, δ) : 1.1-1.4 (12H, m), 2.2-2.6 (4H, m),
2.8-3.6 (12H, m), 4.25 (4H, q, J=7Hz), 4.51 (6H,
s), 5.3-5.6 (2H, m), 6.5-6.6 (2H, m), 6.7-6.8
(2H, m), 6.96 (2H, d, J=8Hz), 7.2-7.4 (6H, m),
7.46 (2H, br s), 8.0-8.3 (1H, m), 8.4-8.8 (1H,
m), 9.8-10.1 (1H, m), 10.2-10.4 (1H, m)

20 FAB-MASS (m/z) : 420 ($MH^+ + 2-HCl$), 418 ($MH^+ - HCl$)

Example 12

25 A solution of (R)-3-chlorostyrene oxide (111 mg) and
7-ethoxycarbonylmethoxy-2-methyl-1,2,3,4-tetrahydro-2-
naphthylamine (190 mg) in ethanol (1.5 ml) was refluxed
for 3 hours. After cooling, the solution was evaporated
in vacuo. The residue was purified by column
30 chromatography on silica gel with a mixture of chloroform
and methanol (100:1) as an eluent to afford a mixture of
(1R,2'R)- and (1R,2'S)-1-(3-chlorophenyl)-2-[(7-ethoxy-
carbonylmethoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)-
amino]ethanol (138 mg) as an oil. The obtained compound
was dissolved in ethyl acetate and to the solution was
35 added a solution of oxalic acid (26 mg) in ethyl acetate
and the whole was evaporated in vacuo. The residue was

trituated with diethyl ether and ethyl acetate to afford a mixture of (1R,2'R)- and (1R,2'S)-1-(3-chlorophenyl)-2-[[7-ethoxycarbonylmethoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthyl)amino]ethanol oxalate.

5 mp : 127-140°C

IR (Nujol) : 3460, 3200, 2800-2300, 1755 cm⁻¹

NMR (DMSO-d₆, δ) : 1.21 (3H, t, J=7.1Hz), 1.24 (3H, s), 1.79-2.20 (2H, m), 2.57-3.45 (6H, m), 4.16 (2H, q, J=7.1Hz), 4.72 (2H, s), 4.98 (1H, d, J=9.2Hz), 5.60-8.50 (4H, br m), 6.64 (1H, s), 6.72 (1H, d, J=8.4Hz), 7.04 (1H, d, J=8.4Hz), 7.32-7.63 (4H, m)

10

Example 13

15 A mixture of 2-bromo-3'-chlorobutyrophenone (262 mg) and (S)-2-amino-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene (748 mg) in methanol (2 ml) was stirred at 45°C for 3.5 hours and the solution was standing at ambient temperature overnight. The solution was evaporated in vacuo and to the residue were added saturated sodium hydrogencarbonate and ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of chloroform and methanol (1:0 - 20:1) as an eluent to afford 2-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]-3'-chlorobutyrophenone (208 mg) as an oil.

20

25

IR (Film) : 1745, 1730 cm⁻¹

30

To a solution of the above obtained compound (198 mg) in ethanol (2 ml) was added sodium borohydride (17 mg) and stirred for 1 hour. To the solution was added 1N hydrochloric acid (3 ml) and the mixture was made alkaline with 1N sodium hydroxide solution. The mixture was

35

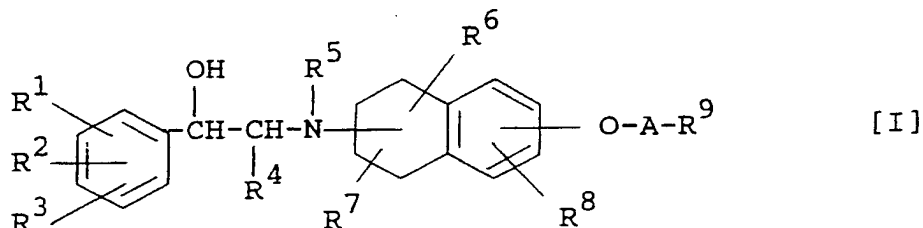
evaporated in vacuo and brine and ethyl acetate were added to the residue. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of chloroform and methanol (300:1) as an eluent to afford a mixture of (1R,2'S)- and (1S,2'S)-1-(3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)amino]butanol (53 mg) as an oil. To a solution of the obtained compound (52 mg) in ethyl acetate was added a solution of oxalic acid (11 mg) in ethyl acetate and the whole was evaporated in vacuo. The residue was triturated with diethyl ether to afford a mixture of (1R,2'S)- and (1S,2'S)-1-(3-chlorophenyl)-2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl)-amino]butanol oxalate.

mp : 159-164°C

IR (Nujol) : 3300, 1740, 1725 cm⁻¹

C L A I M S

1. A compound of the formula :



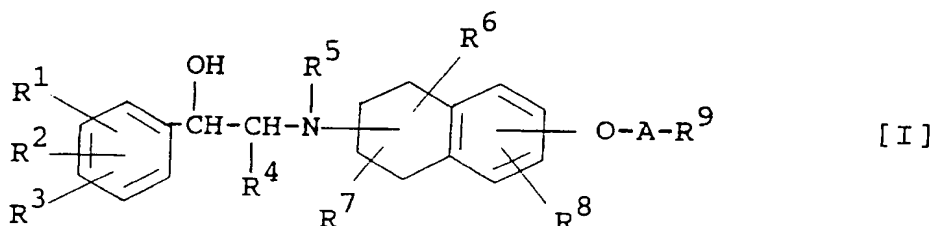
10 wherein R^1 is hydrogen or halogen,
 R^2 is halogen, hydroxy, protected hydroxy,
 aryloxy, lower alkoxy, halo(lower)-
 alkoxy, nitro, cyano, amino or
 15 acylamino,
 R^3 is hydrogen or halogen,
 R^4 is hydrogen or lower alkyl,
 R^5 is hydrogen or lower alkyl,
 R^6 is hydrogen, hydroxy or lower alkyl,
 20 R^7 is hydrogen or lower alkyl,
 R^8 is hydrogen or halogen,
 R^9 is carboxy or esterified carboxy, and
 A is lower alkylene,
 provided that R^4 is lower alkyl; R^5 is lower
 25 alkyl; R^6 is hydroxy or lower alkyl;
 or R^8 is halogen when R^1 is hydrogen, R^2 is
 halogen and R^3 is hydrogen,
 and pharmaceutically acceptable salt thereof.

- 30 2. A compound according to claim 1,
 wherein R^4 is hydrogen and
 R^5 is hydrogen.

- 35 3. A compound according to claim 2,
 wherein R^7 is hydrogen and

R^8 is hydrogen.

4. A compound according to claim 3,
 wherein R^1 is halogen,
 R^2 is halogen, hydroxy or protected hydroxy,
 R^3 is hydrogen,
 R^6 is hydrogen or hydroxy, and
 R^9 is lower alkoxy carbonyl.
5. A compound of claim 4, which is
 (-)-1-(3-chloro-4-hydroxyphenyl)-2-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-2-naphthyl]-amino]ethanol or its hydrochloride.
6. A process for preparing a compound of the formula :

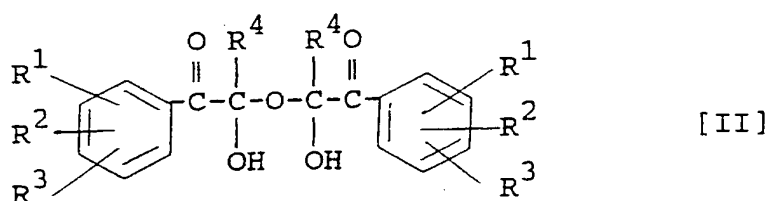


- wherein R^1 is hydrogen or halogen,
 R^2 is halogen, hydroxy, protected hydroxy,
 aryloxy, lower alkoxy,
 halo(lower)alkoxy,
 nitro, cyano, amino or acylamino,
 R^3 is hydrogen or halogen,
 R^4 is hydrogen or lower alkyl,
 R^5 is hydrogen or lower alkyl,
 R^6 is hydrogen, hydroxy or lower alkyl,
 R^7 is hydrogen or lower alkyl,
 R^8 is hydrogen or halogen,
 R^9 is carboxy or esterified carboxy, and
 A is lower alkylene,

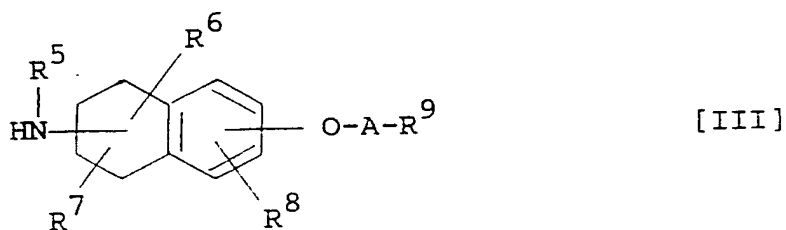
provided that R^4 is lower alkyl; R^5 is lower alkyl; R^6 is hydroxy or lower alkyl; or R^8 is halogen when R^1 is hydrogen, R^2 is halogen and R^3 is hydrogen,

or pharmaceutically acceptable salt thereof, which comprises,

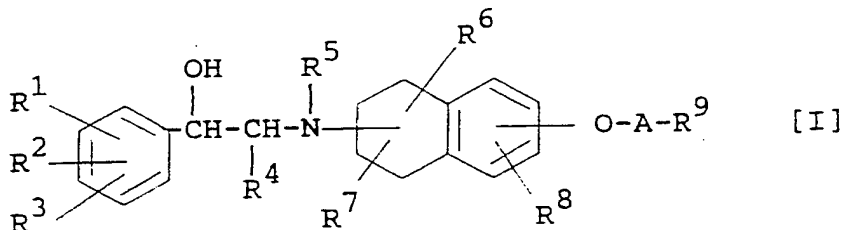
a) reacting a compound of the formula :



or its salt with a compound of the formula :

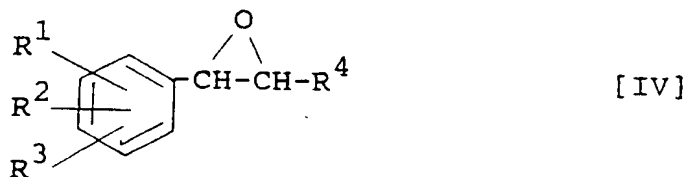


or its salt in the presence of a reducing agent to provide a compound of the formula :

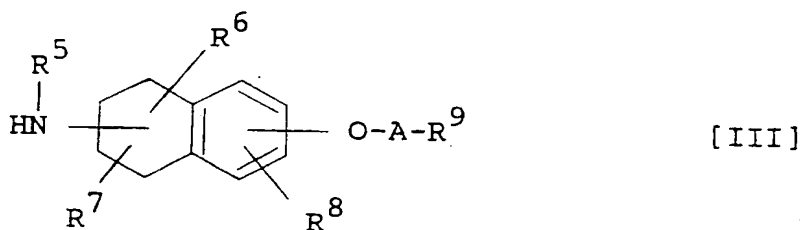


or its salt, in the above formulas, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and A are each as defined above, or

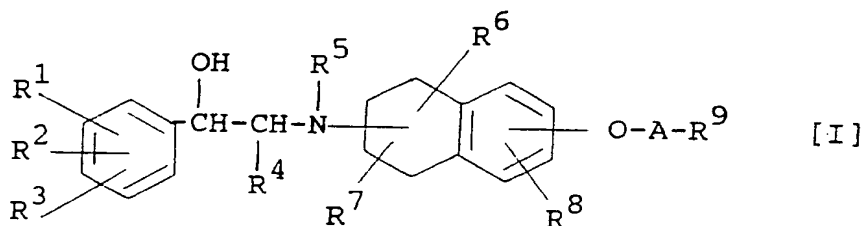
b) reacting a compound of the formula :



or its salt with a compound of the formula :

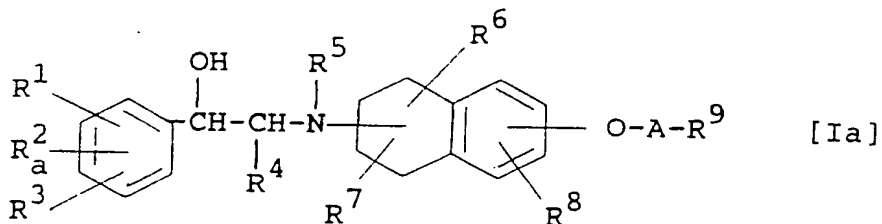


or its salt to provide a compound of the formula :

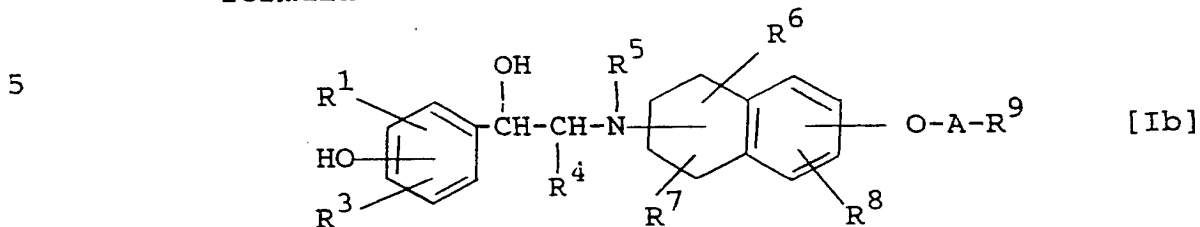


25 or its salt, in the above formulas, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and A are each as defined above, or

c) subjecting a compound of the formula :

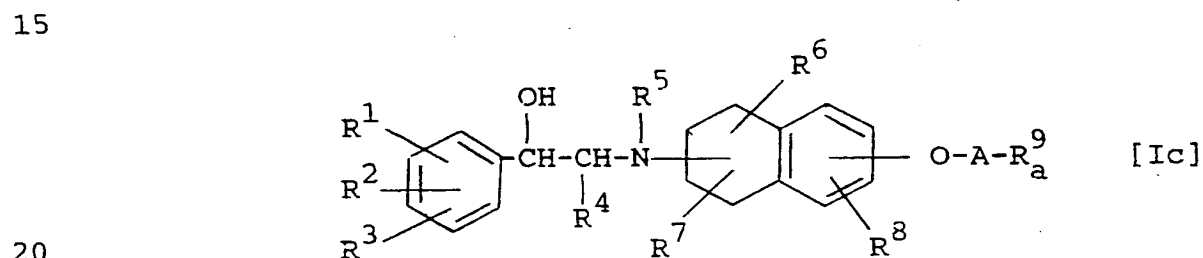


or its salt to elimination reaction of the hydroxy-protective group to provide a compound of the formula :

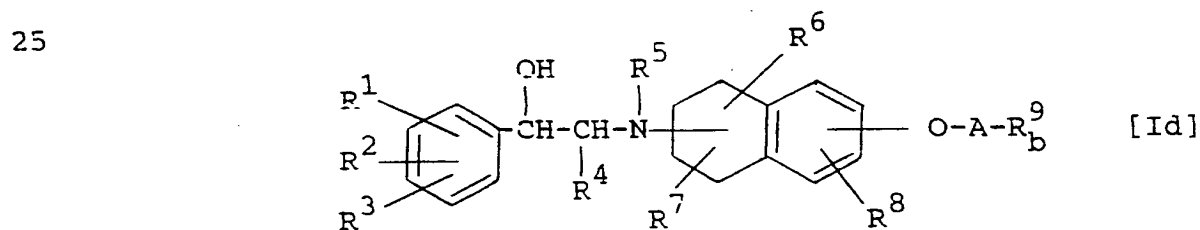


10 or its salt, in the above formulas, R_a^2 is protected hydroxy, and R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and A are each as defined above, or

15 d) subjecting a compound of the formula :



or its salt to deesterification reaction to provide a compound of the formula :

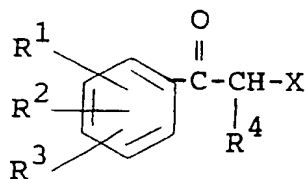


30 or its salt, in the above formulas, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and A are each as defined above,

35 R_a^9 is esterified carboxy, and R_b^9 is carboxy, or

e) reacting a compound of the formula :

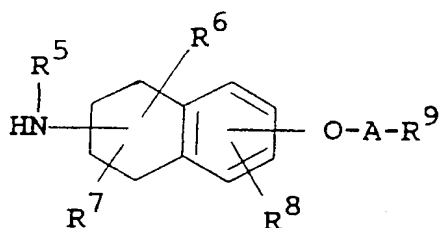
5



[V]

or its salt with a compound of the formula :

10

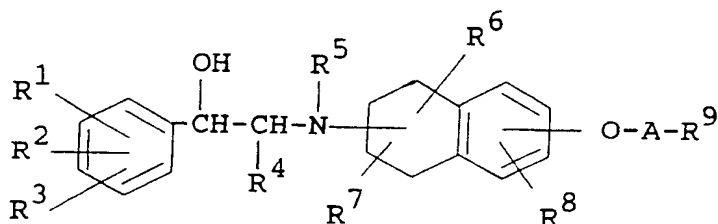


[III]

15

or its salt, and then subjecting the resultant product to reduction to provide a compound of the formula :

20



[I]

25

or its salt, in the above formulas,
 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and A are each as defined above, and X is halogen.

30

7. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

35

8. A compound of claim 1 for use as a medicament.

9. A method for therapeutic treatment and/or prevention of dysuria, spasm or hyperanakinosis which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

5

10. Use of a compound of claim 1 for the manufacture of a medicament for the treatment and/or prevention of dysuria, spasm or hyperanakinosis in human beings or animals.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 92/00449

I. CLASSIFICATION OF SUBJECT MATTER (Several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
Int.Cl.5 C 07 C 217/74

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System

Classification Symbols

Int.Cl.5

C 07 C 217/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0303546 (MIDY S.p.A) 15 February 1989, see examples 3-8,12-15; claims (cited in the application) ---	1-10
X	Chemical Abstracts, vol. 111, no. 17, 23 October 1989, (Columbus, Ohio, US), L. MANARA et al.: "New developments in beta-adrenergic-mediated control of intestinal motility: gut-specific phenylethanolami notetralines", see page 12, column 2, abstract no. 146279e, & FIDIA RES. FOUND. SYMP. SER. 1989, 2(NEUROCHEM. PHARMACOL.-TRIBUTE B.B. BRODIE), 131-47, see abstract ---	1-10
A	EP,A,0303545 (MIDY S.p.A.) 15 February 1989, see examples; claims --- -/-	1-10

¹⁰ Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

06-08-1992

Date of Mailing of this International Search Report

19.08.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Natalie Weinberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
1 A	EP,A,0211721 (SANOFI) 25 February 1987, see examples; claims ---	1-10
5 A	EP,A,0403360 (SANOFI) 19 December 1990, see claims ---	1-10
5 A	EP,A,0383686 (SANOFI) 22 August 1990, see examples; claims (cited in the application) -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 92/00449

Box I Observations where certain claims were found unsearchable (Continuation of item 5 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 9 has been drawn to a method of treatment of the human or animal body by therapy (Art.52(4)EPC) the search has been carried out based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9200449
SA 58229

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